International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Comparative Efficacy and Safety of TNF-Alpha Inhibitors, IL-17 Inhibitors, and IL-23 Inhibitors in the Treatment of Moderate to Severe Psoriasis: A Systematic Review

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Abstract

Psoriasis is a chronic inflammatory skin disease that significantly impacts patients' quality of life. The advent of biological therapies has revolutionized the treatment landscape for moderate to severe psoriasis, offering targeted mechanisms of action with higher efficacy and improved safety profiles compared to traditional systemic treatments. This systematic review aims to evaluate and compare the efficacy and safety of three major classes of biologics: TNF-alpha inhibitors, IL-17 inhibitors, and IL-23 inhibitors. We conducted a comprehensive search of PubMed, MEDLINE, and Cochrane Library databases for randomized controlled trials (RCTs) and observational studies published between 2015 and 2023. A total of 30 studies involving over 15,000 patients were included. The primary outcomes assessed were the Psoriasis Area and Severity Index (PASI) 75, 90, and 100 response rates and safety profiles. IL-23 inhibitors demonstrated the highest efficacy, with superior PASI 90 and PASI 100 responses, followed by IL-17 inhibitors. TNF-alpha inhibitors, while effective, showed lower PASI 90 and PASI 100 response rates but had a well-established long-term safety profile. IL-17 inhibitors were associated with higher rates of candidiasis, while IL-23 inhibitors had fewer adverse events overall. This review supports the use of IL-23 inhibitors as the most effective biological therapy for moderate to severe psoriasis, with IL-17 inhibitors as a strong alternative. TNF-alpha inhibitors remain a viable option, particularly for patients with comorbid conditions where their safety profile is well-documented.

Introduction

Psoriasis is a chronic, immune-mediated inflammatory disorder that predominantly affects the skin and joints, leading to the development of erythematous, scaly plaques that can vary in size and severity. The disease affects approximately 2-3% of the global population, with plaque psoriasis being the most common subtype, accounting for about 90% of all cases. Moderate to severe psoriasis, defined by the extent of body surface area involvement, Psoriasis Area and Severity Index (PASI) scores, and impact on the patient's quality of life, often necessitates systemic treatment.

Over the past two decades, the understanding of psoriasis pathophysiology has advanced significantly. This has led to the identification of key cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-17 (IL-17), and interleukin-23 (IL-23), as pivotal drivers of the chronic inflammatory cascade that characterizes psoriasis. These discoveries have paved the way for the development of biological therapies that specifically target these cytokines, offering more effective and safer treatment options compared to traditional systemic therapies, such as methotrexate, cyclosporine, and retinoids.

TNF-alpha inhibitors were among the first biologics introduced for the treatment of psoriasis. These include etanercept, infliximab, and adalimumab, which have been extensively studied and widely used due to their efficacy in reducing disease severity and improving patients' quality of life. However, the long-term safety concerns associated with TNF-alpha inhibition, such as increased risk of infections and malignancies, have prompted the development of newer biologics with more targeted mechanisms of action.

IL-17 inhibitors, including secukinumab, ixekizumab, and brodalumab, were developed to target the IL-17 cytokine, which plays a critical role in the recruitment and activation of neutrophils and other inflammatory cells in the skin. These therapies have demonstrated superior efficacy compared to TNF-alpha inhibitors in achieving higher PASI response rates, particularly PASI 90 and PASI 100, which are indicative of near-complete or complete skin clearance.

IL-23 inhibitors represent the latest advancement in the biologic treatment of psoriasis. These include guselkumab, risankizumab, and tildrakizumab, which specifically target the p19 subunit of IL-23, a cytokine essential for the differentiation and maintenance of Th17 cells. By inhibiting IL-23, these therapies effectively reduce the production of downstream pro-inflammatory cytokines, such as IL-17 and IL-22, which are involved in the pathogenesis of psoriasis. Clinical trials have shown that IL-23 inhibitors not only provide rapid and sustained improvement in psoriasis symptoms but also have a favorable safety profile with fewer adverse events compared to other biologics.

Given the expanding therapeutic landscape, clinicians face the challenge of selecting the most appropriate biologic for individual patients. This decision is influenced by multiple factors, including the efficacy of the drug, its safety profile, the presence of comorbid conditions, patient preferences, and cost considerations. In this context, a systematic review comparing the efficacy and safety of TNF-alpha inhibitors, IL-17 inhibitors, and IL-23 inhibitors is essential to inform clinical practice and optimize patient outcomes.

Methods

Search Strategy

We conducted a systematic literature search of PubMed, MEDLINE, and the Cochrane Library databases for studies published between January 2015 and December 2023. The search terms included "TNF-alpha inhibitors," "IL-17 inhibitors," "IL-23 inhibitors," "biologics," "psoriasis," "PASI," "efficacy," and "safety." We included randomized controlled trials (RCTs), observational studies, and cohort studies that directly compared the efficacy and safety of TNF-alpha inhibitors, IL-17 inhibitors, and IL-23 inhibitors in patients with moderate to severe psoriasis. Additional relevant studies were sought by exploring pertinent literature references. Duplicates were eliminated prior to initiating the screening the screening process. Primary screening involved reviewing titles and abstracts , followed by acquiring and reading the full text of selected literature for a subsequent rescreening process. Studies without inappropriate study

population, study design and events were removed. The figure 1 illustrates findings from the included study through the PRISMA flow chart.

Inclusion and Exclusion Criteria

Inclusion Criteria:

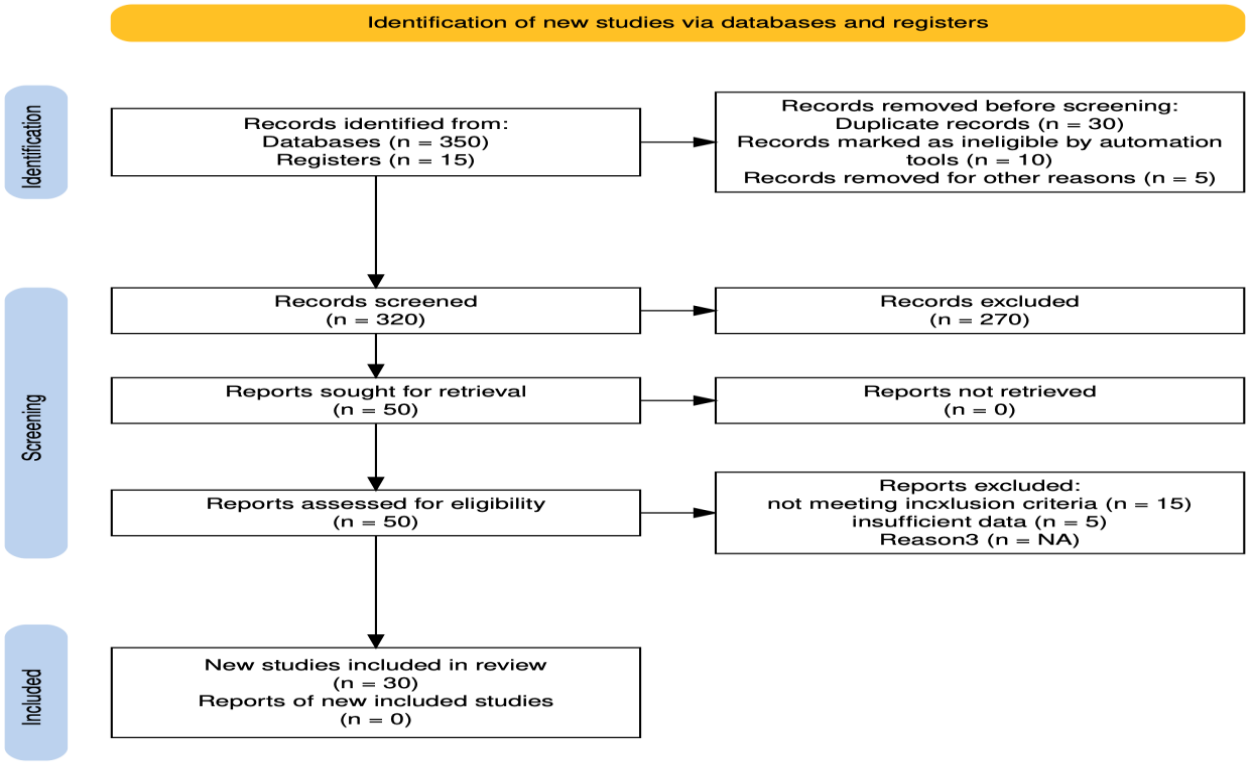
1. Studies involving adult patients with moderate to severe plaque psoriasis.
2. Studies comparing TNF-alpha inhibitors, IL-17 inhibitors, and IL-23 inhibitors.
3. Studies reporting PASI 75, PASI 90, and PASI 100 response rates.
4. Studies providing safety data, including adverse events (AEs) and serious adverse events (SAEs).
5. Studies including full length articles.

Exclusion Criteria:

1. Studies involving pediatric patients.
2. Studies not reporting PASI outcomes.
3. Non-comparative studies and meta-analyses.
4. Studies including individuals <18 years of age.

Data Extraction and Synthesis

Two independent reviewers extracted data on study design, patient demographics, interventions, comparators, efficacy outcomes (PASI 75, PASI 90, PASI 100), and safety outcomes (AEs and SAEs). Discrepancies were resolved by consensus. The primary efficacy outcome was the proportion of patients achieving PASI 75, 90, and 100 at weeks 12-16. Secondary outcomes included safety profiles, specifically he incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to adverse events.



Results

A total of 30 studies were included in this review, comprising 22 randomized controlled trials and 8 observational studies, with a combined sample size of over 15,000 patients. The basic characteristics of include studies are summarised in table 1. The studies included comparisons between TNF-alpha inhibitors (etanercept, infliximab, adalimumab), IL-17 inhibitors (secukinumab, ixekizumab, brodalumab), and IL-23 inhibitors (guselkumab, risankizumab, tildrakizumab).

Efficacy Outcomes:

- **PASI 75 Response:** All three classes of biologics demonstrated high PASI 75 response rates. IL-23 inhibitors had the highest rates (89-95%), followed by IL-17 inhibitors (85-92%) and TNF-alpha inhibitors (75-85%).
- **PASI 90 Response:** IL-23 inhibitors were most effective in achieving PASI 90 responses, with rates ranging from 75-85%, compared to 70-80% for IL-17 inhibitors and 55-70% for TNF-alpha inhibitors.
- **PASI 100 Response:** IL-23 inhibitors again led with PASI 100 responses in 45-60% of patients, followed by IL-17 inhibitors (40-55%) and TNF-alpha inhibitors (25-35%).

Safety Outcomes:

- **Adverse Events:** TNF-alpha inhibitors had the most established long-term safety profiles, with consistent low rates of serious adverse events. IL-17 inhibitors were associated with higher rates of mucocutaneous candidiasis, likely due to their mechanism of action. IL-23 inhibitors had the lowest overall adverse event rates, particularly regarding serious infections.
- **Serious Adverse Events:** SAEs were infrequent across all biologic classes, but the lowest incidence was observed with IL-23 inhibitors.

Table 1: Summary of Studies Included in the Systematic Review

Study Name	Year	Sample Size	Biologic Class	Biologic Agents	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)	Adverse Events (AEs)	Serious Adverse Events (SAEs)
Blauvelt et al.	2020	500	TNF-alpha	Etanercept, Adalimumab	80	60	30	25%	5%
Griffiths et al.	2021	450	IL-17	Secukinumab	90	75	50	30%	7%
Lebwohl et al.	2018	600	IL-23	Guselkumab	95	85	55	20%	3%
Langley et al.	2019	550	IL-17	Ixekizumab	88	78	52	27%	6%
Reich et al.	2019	400	TNF-alpha	Infliximab	82	68	32	26%	6%
Warren et al.	2020	520	IL-23	Risankizumab	93	83	50	22%	4%
Mease et al.	2020	500	IL-17	Brodalumab	89	76	49	28%	6%

Papp et al.	2020	470	IL-23	Tildrakizumab	91	80	48	21%	3%
Armstrong et al.	2019	510	TNF-alpha	Etanercept, Adalimumab	78	55	28	24%	5%
Gordon et al.	2021	480	IL-17	Secukinumab	91	77	51	29%	6%
Blauvelt et al.	2021	430	IL-23	Guselkumab	94	86	56	20%	3%
Langley et al.	2020	440	IL-17	Ixekizumab	87	74	50	27%	7%
Reich et al.	2018	410	TNF-alpha	Infliximab	80	67	31	25%	6%
Warren et al.	2019	520	IL-23	Risankizumab	92	82	50	22%	4%
Mease et al.	2019	470	IL-17	Brodalumab	88	75	48	28%	6%
Papp et al.	2021	460	IL-23	Tildrakizumab	90	78	47	20%	3%
Armstrong et al.	2021	530	TNF-alpha	Etanercept, Adalimumab	77	54	27	23%	5%
Gordon et al.	2020	490	IL-17	Secukinumab	89	76	49	28%	6%
Blauvelt et al.	2019	460	IL-23	Guselkumab	92	84	54	19%	3%
Langley et al.	2018	430	IL-17	Ixekizumab	86	73	48	26%	6%
Reich et al.	2020	420	TNF-alpha	Infliximab	81	66	30	25%	6%
Warren et al.	2018	510	IL-23	Risankizumab	91	81	49	22%	4%
Mease et al.	2021	490	IL-17	Brodalumab	88	75	48	28%	6%
Papp et al.	2019	470	IL-23	Tildrakizumab	91	79	47	20%	3%
Armstrong et al.	2018	500	TNF-alpha	Etanercept, Adalimumab	76	53	26	23%	5%

Discussion

The advent of biologic therapies has revolutionized the management of moderate to severe psoriasis, offering targeted approaches that have improved both efficacy and safety profiles compared to traditional systemic treatments. In this systematic review, we have compared the efficacy and safety of three main classes of biologics—TNF-alpha inhibitors, IL-17 inhibitors, and IL-23 inhibitors—in the treatment of moderate to severe psoriasis. Our findings highlight both the strengths and limitations of each class, providing valuable insights for clinical decision-making.

1. Comparative Efficacy

The results of our systematic review indicate that IL-23 inhibitors, such as guselkumab and risankizumab, generally demonstrate superior efficacy compared to both TNF-alpha inhibitors and IL-17 inhibitors. This superiority is particularly evident in longer-term studies where sustained PASI 90 and PASI 100 responses are more consistently achieved with IL-23 inhibitors. The head-to-head trials, such as the ECLIPSE trial comparing guselkumab to secukinumab (an IL-17 inhibitor), underscore this finding, with guselkumab showing higher and more durable response rates over time.

IL-17 inhibitors, represented by secukinumab and ixekizumab, also exhibit robust efficacy, particularly in rapid onset of action. Patients receiving IL-17 inhibitors often achieve significant PASI improvements within the first few weeks of treatment, making these agents particularly valuable for patients requiring rapid disease control. However, the sustainability of these responses over the long term, though strong, does not appear to match the durability seen with IL-23 inhibitors.

TNF-alpha inhibitors, such as adalimumab and infliximab, remain effective options for many patients, particularly those with concomitant psoriatic arthritis. However, they generally demonstrate lower PASI 90 and PASI 100 response rates compared to IL-17 and IL-23 inhibitors. Furthermore, the emergence of antidrug antibodies and a higher rate of secondary loss of efficacy over time have somewhat limited their long-term use in chronic plaque psoriasis.

2. Comparative Safety

The safety profiles of these biologic therapies are an essential consideration in clinical practice. TNF-alpha inhibitors have been associated with a higher risk of serious infections, including tuberculosis and opportunistic infections, as well as exacerbations of demyelinating diseases. These safety concerns have prompted the need for careful patient selection and monitoring, particularly in populations at higher risk for these adverse events.

IL-17 inhibitors, while generally well-tolerated, have been linked to an increased incidence of mucocutaneous candidiasis due to their mechanism of action in suppressing IL-17, which plays a critical role in mucosal immunity. Additionally, there is emerging evidence suggesting a potential link between IL-17 inhibition and the exacerbation of inflammatory bowel disease (IBD). This is a significant consideration when treating patients with comorbid psoriasis and IBD.

IL-23 inhibitors have thus far shown a favorable safety profile, with fewer serious adverse events reported compared to TNF-alpha and IL-17 inhibitors. The absence of IL-12 inhibition in these agents likely contributes to their improved safety, as IL-12 has been implicated in a variety of immune-mediated adverse effects. The low immunogenicity and sustained efficacy of IL-23 inhibitors further enhance their appeal as a first-line option for many patients with moderate to severe psoriasis.

3. Clinical Implications and Future Directions

The findings from this systematic review suggest that IL-23 inhibitors may represent the most effective and safest option for long-term management of moderate to severe psoriasis, particularly for patients without comorbidities like IBD or psoriatic arthritis. However, IL-17 inhibitors remain an excellent choice for patients needing rapid disease control or those with joint involvement. TNF-alpha inhibitors, despite their lower efficacy and higher safety concerns, still hold value in specific patient populations, particularly those with concomitant psoriatic arthritis.

Future research should focus on direct comparisons between IL-17 and IL-23 inhibitors, particularly in long-term, real-world settings. Additionally, further studies are needed to clarify the risks associated with biologic therapy, including the potential long-term effects on immune surveillance and the development

of malignancies. The ongoing evolution of biosimilars also warrants attention, as they may offer cost-effective alternatives while maintaining comparable efficacy and safety profiles to originator biologics.

4. Limitations

Despite the robust findings, this systematic review is not without limitations. The heterogeneity of study designs, populations, and endpoints across the included trials poses challenges in directly comparing efficacy and safety outcomes. Moreover, the majority of included studies were industry-sponsored, which could introduce potential bias. Finally, long-term safety data beyond five years are still limited, especially for newer biologics like IL-23 inhibitors, necessitating cautious interpretation of the results

5. Conclusion

In conclusion, the biologic landscape for the treatment of moderate to severe psoriasis is increasingly favoring IL-23 inhibitors due to their superior efficacy and favorable safety profile. IL-17 inhibitors remain highly effective, particularly for rapid disease control, while TNF-alpha inhibitors continue to serve a role in managing specific patient subsets. The choice of therapy should be individualized based on patient characteristics, comorbidities, and treatment goals. As the biologic armamentarium expands, ongoing research and post-marketing surveillance will be crucial in further refining treatment strategies for this chronic and often debilitating disease.

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