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The Analysis Study of Effectiveness and Safety of Rituximab in The Management of Pediatric Systemic Lupus Erythematosus: A Systematic Review

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ABSTRACT

Background: Pediatric systemic lupus erythematosus (pSLE) is a chronic autoimmune disease with an incidence of 0.3–0.9 per 100,000 children per year. Despite growing interest in RTX as a therapeutic option, its use in pSLE remains off-label, and its efficacy and safety have not been well established in this population. This systematic review aims to assess the effectiveness and safety of RTX in children with pSLE based on literatures of the last decade. **Methods:** The study followed PRISMA 2020 guidelines, reviewing English-language publications from 2015 to 2025. Editorials, duplicate reviews from the same journal, and papers lacking a DOI were excluded. The literature search was conducted using PubMed, SagePub, SpringerLink, and Google Scholar. **Result:** A total of 2,172 articles were initially identified through online databases (PubMed, SagePub, SpringerLink, and Google Scholar). After three rounds of screening, eight relevant studies were selected for full-text analysis. **Conclusion:** Rituximab is an effective and well-tolerated treatment for pediatric SLE, reducing disease activity, corticosteroid dependence, and flare-ups. While generally safe, monitoring for infusion reactions and hypogammaglobulinemia is crucial. Early administration may improve outcomes, highlighting its role in refractory pediatric SLE management.

Keyword: rituximab, systemic lupus erythematosus, pediatric, efficacy, safety

INTRODUCTION

Pediatric systemic lupus erythematosus (pSLE) is a chronic autoimmune disease with an incidence of 0.3–0.9 per 100,000 children per year and a prevalence of 3.3–8.8 per 100,000 children. Compared to adult-onset systemic lupus erythematosus (SLE), pSLE is often characterized by a more aggressive disease course, with higher rates of organ involvement, particularly affecting the kidneys and central nervous system. These complications contribute to significant morbidity and necessitate the use of effective therapeutic strategies to control disease activity and prevent long-term damage.^{1,2}

Current treatment approaches for pSLE primarily rely on corticosteroids and conventional immunosuppressive agents such as mycophenolate mofetil, azathioprine, and cyclophosphamide. While these therapies can help manage symptoms and reduce disease flares, their efficacy in severe or refractory cases remains suboptimal. Furthermore, prolonged use of corticosteroids and immunosuppressants is associated with substantial adverse effects,

including growth impairment, osteoporosis, and increased susceptibility to infections. These limitations highlight the need for targeted therapies that can provide better disease control with a more favorable safety profile.^{3,4}

B-lymphocytes play a central role in the pathogenesis of SLE by contributing to autoantibody production, antigen presentation, and cytokine secretion. Given their crucial involvement in disease progression, B-cell depletion has emerged as a promising therapeutic strategy. Rituximab (RTX), a chimeric monoclonal IgG1 kappa antibody that selectively targets the CD20 antigen on B cells, has gained attention as a potential treatment option for pSLE. By depleting B cells, RTX disrupts autoantibody production and modulates immune system activity, which may lead to clinical improvements in patients with refractory disease.^{5,6}

Despite growing interest in RTX as a therapeutic option, its use in pSLE remains off-label, and its efficacy and safety have not been well established in this population. Although some reports suggest that

RTX may be beneficial in patients who do not respond to standard immunosuppressive therapy, concerns persist regarding the risk of severe infections, infusion reactions, and long-term immunosuppression. Additionally, there is a lack of consensus regarding optimal dosing regimens and patient selection criteria for RTX therapy in pSLE.^{7,8}

Given these uncertainties, a systematic evaluation of the available evidence is crucial to determine the clinical benefits and risks of RTX in pSLE management. This systematic review aims to assess the effectiveness and safety of RTX in children with pSLE by analyzing published literature on treatment outcomes, adverse effects, and overall therapeutic impact. By evaluating the current evidence, this review seeks to inform clinicians and researchers about the potential role of RTX in pSLE management and identify gaps that require further investigation.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines

to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to assess the effectiveness and safety of RTX in children with pSLE based on literatures of the last decade. The review aimed to provide insights to improve patient treatment strategies, with an emphasis on the significance of key findings in the reviewed studies. Inclusion criteria for the study included: 1) Papers published in English, and 2) Papers published between 2014 and 2024. Exclusion criteria were: 1) Editorials, 2) Papers without a DOI, 3) Previously published review articles, and 4) Duplicate entries in journals.

Search Strategy

The keywords used for this research are rituximab, systemic lupus erythematosus, pediatric, efficacy, safety. The Boolean MeSH keywords inputted on databases for this research are:
((("rituximab"[MeSH Terms] OR

*"rituximab"[All Fields] OR
"rituximab s"[All Fields]) AND
("lupus erythematosus,
systemic"[MeSH Terms] OR
("lupus"[All Fields] AND
"erythematosus"[All Fields] AND
"systemic"[All Fields]) OR "systemic
lupus erythematosus"[All Fields] OR
("systemic"[All Fields] AND
"lupus"[All Fields] AND
"erythematosus"[All Fields])) AND
("paediatrics"[All Fields] OR
"pediatrics"[MeSH Terms] OR
"pediatrics"[All Fields] OR
"paediatric"[All Fields] OR
"pediatric"[All Fields]) AND
("efficacies"[All Fields] OR
"efficacious"[All Fields] OR
"efficaciously"[All Fields] OR
"efficaciousness"[All Fields] OR
"efficacy"[All Fields])) OR
("safety"[MeSH Terms] OR
"safety"[All Fields] OR "safeties"[All
Fields])) AND (y_10[Filter])*

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further

analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	((("rituximab"[MeSH Terms] OR "rituximab"[All Fields] OR "rituximab s"[All Fields]) AND ("lupus erythematosus, systemic"[MeSH Terms] OR ("lupus"[All Fields] AND "erythematosus"[All Fields] AND "systemic"[All Fields]) OR "systemic lupus erythematosus"[All Fields] OR ("systemic"[All Fields] AND "lupus"[All Fields] AND "erythematosus"[All Fields])) AND ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND ("efficacies"[All Fields] OR "efficacious"[All Fields] OR "efficaciously"[All Fields] OR "efficaciousness"[All Fields] OR "efficacy"[All Fields])) OR ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields])) AND (y 10[Filter])	466
Springer Link	((((rituximab) AND (systemic lupus erythematosus)) AND (pediatric)) AND (efficacy)) OR (safety)	402
Sagepub	((((rituximab) AND (systemic lupus erythematosus)) AND (pediatric)) AND (efficacy)) OR (safety)	500
Google Scholar	((((rituximab) AND (systemic lupus erythematosus)) AND (pediatric)) AND (efficacy)) OR (safety)	804

Table 2. JBI *Critical appraisal of Study*

Parameters	Sawhney (2021)	Tambralli (2015)	Wats on (2015)	Alexeeva (2016)	Alsu baie (2024)	Lin (2024)	Ko (2020)	Ol f at (2015)
1. Bias related to temporal precedence								
Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation								
Was there a control group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Bias related to administration of intervention/exposure								
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No.	No.	No.	No.	No.	No.	No.	No.
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes of participants included in any comparisons measured in the same way?	No.	No.	No.	No.	No.	No.	No.	No.
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

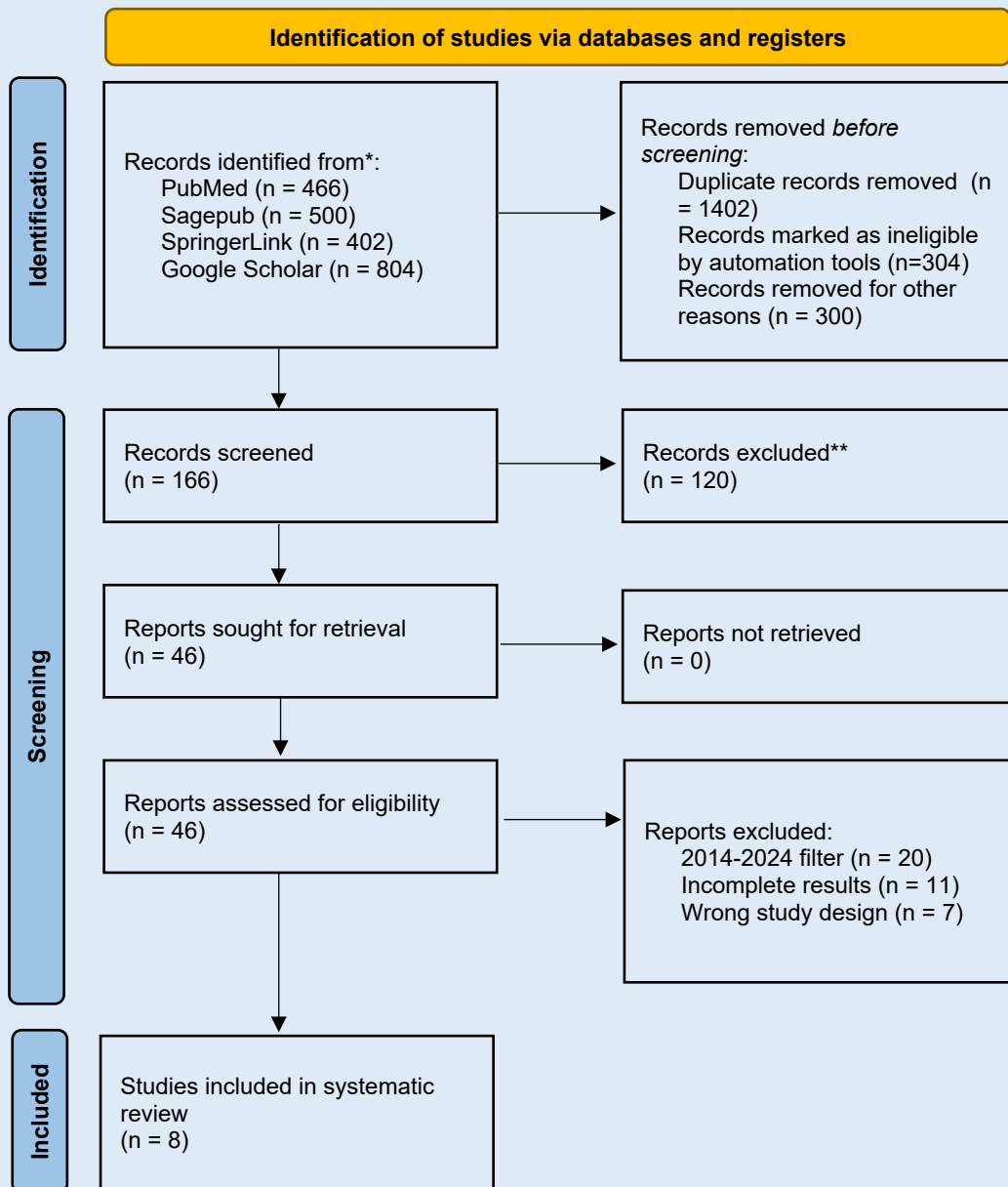


Figure 1. Article search flowchart

RESULT

The initial number of articles retrieved from online databases (PubMed, SagePub, SpringerLink, and Google Scholar) is 2,172 articles. After conducting three levels of screening, eight articles that directly relate to the current systematic review have been chosen for further assessment through full-text reading and analysis. Table 3 presents the selected literature included in this analysis.

Table 3. The literature included in this study

No.	Author	Origin	Method	Sample	Result
1.	Sawhney, et al. ⁹ (2021)	India	Retrospective cohort	225	RTX was administered to 17 out of 225 pediatric lupus patients (7.5%), primarily for resistant renal disease (53%). Significant clinical improvements were observed, with the mean SLEDAI score dropping from 16.25 to 1.43 at six months ($p=0.001$) and steroid use decreasing from 100% to 33% at two years. Nephritis patients showed a sustained reduction in proteinuria, with the urine spot protein-creatinine ratio decreasing from 3.1 to 0.4 at one year ($p=0.006$). Notably, 82% of patients remained flare-free over a median follow-up of 24 months, and no adverse events were reported.
2.	Tambralli, et al. ¹⁰ (2015)	USA	Retrospective cohort	104	In a study of 104 children, including 50 with SLE, RTX treatment led to improvements in corticosteroid dosage, physician-assessed disease activity, and SLE-related disease markers. The incidence of hospitalized infections was comparable

					to previous reports on childhood-onset SLE.
3.	Watson, et al. ¹¹ (2015)	UK	Retrospective cohort	63	In a 10-year study, 63 pediatric lupus patients received 104 courses of RTX, with lupus nephritis being the most common indication (36%). Significant improvements were observed in ESR, complement levels (C3, C4), creatinine, albumin, hemoglobin, anti-dsDNA titers, and urine albumin-creatinine ratio within 2.5 months post-treatment. Corticosteroid dosage was also significantly reduced ($p=0.01$). Adverse events were reported in 18% of courses, including delayed second doses (8%), infusion reactions (6%), and anaphylaxis (2%). While the global BILAG score showed a trend toward improvement, controlled studies are needed to confirm these findings.
4.	Alexeeva, et al. ¹² (2016)	Russia	Retrospective cohort	12	In a study of 12 pediatric SLE patients treated with RTX for up to 48 weeks, significant clinical improvements were observed. The SELENA SLEDAI index decreased from 16 to 1 ($p<0.001$), the Damage Index from 3.5 to 1.0 ($p=0.024$), complement C4 levels increased ($p=0.017$), and anti-dsDNA antibody levels significantly decreased ($p=0.004$). Complete B-cell depletion was noted in

					all patients, and prednisolone dosage was reduced from 0.80 to 0.20 mg/kg/day ($p=0.025$). No disease exacerbations occurred, but adverse events included pneumonia ($n=2$), neutropenia ($n=5$), Herpes zoster ($n=2$), and hypogammaglobulinemia ($n=8$).
5.	Alsubaie, et al. ¹³ (2024)	Saudi Arabia	Retrospective cohort	22	In a study of 22 pediatric patients, RTX was primarily used for nephrotic syndrome and SLE, often as a second-line treatment following corticosteroids. The most common protocol involved two infusions of 375 mg/m ² given two weeks apart. Infusion-related adverse events occurred in 31.8% of patients, ranging from mild symptoms like chest tightness, fever, and headache to severe reactions such as anaphylaxis. No infection-related adverse events were reported.
6.	Lin, et al. ¹⁴ (2024)	Taiwan	Retrospective cohort	40	In a study of 40 pediatric SLE patients treated with RTX, the median SLEDAI-2000 score decreased from 8 to 4 over two years. Significant improvements were observed in complement levels (C3, C4) and anti-dsDNA levels within six months, along with a 50% reduction in oral prednisolone dosage. Disease control was achieved in 20% of

					patients, while 87.5% remained flare-free during the median two-year follow-up. Patients who achieved disease control received RTX earlier in their disease course. Adverse events were minimal, with only one case of hypogammaglobulinemia requiring IVIG replacement.
7.	Ko, et al. ¹⁵ (2020)	South Korea	Retrospective cohort	32	This study retrospectively reviewed 32 pediatric patients treated with RTX, though it primarily focused on autoimmune neuroinflammatory diseases rather than SLE. Among the included patients, RTX was associated with clinical improvement, with 82.1% showing a favorable response at the last follow-up.
8.	Olfat, et al. ¹⁶ (2015)	Canada	Retrospective cohort	394	In this study, 6% of childhood-onset SLE (cSLE) patients received rituximab (RTX) for refractory autoimmune cytopenias, including autoimmune thrombocytopenia (AITP) and autoimmune hemolytic anemia (AIHA). A complete response was achieved in most cases, with a median time of 48 days, though 21% experienced flare-ups. RTX was well tolerated, with rare infusion reactions and one herpes zoster infection requiring

					hospitalization. However, persistent hypogammaglobulinemia developed in some patients, particularly those with preexisting low IgG levels.
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Sawhney, et al.⁹ (2021) support the efficacy and safety of RTX in pediatric lupus, particularly in resource-limited settings.

Tambralli, et al.¹⁰ (2015) suggest that RTX is a safe treatment option in children, helping to reduce disease activity and steroid dependence.

Watson, et al.¹¹ (2015) found that rituximab improves disease activity in children with lupus and serious AEs are infrequent.

Alexeeva, et al.¹² (2016) suggest RTX is highly effective with an acceptable risk-benefit profile in refractory pediatric SLE.

Alsubaie, et al.¹³ (2024) highlights both the varied indications for which RTX was prescribed and the need for vigilance concerning infusion-related adverse events. It underscores the importance of close monitoring and appropriate management to ensure the safety of RTX therapy in pediatric patients

Lin, et al.¹⁴ (2024) showed that compared to a control group, RTX-treated patients had superior disease outcomes and fewer flare-ups, with no mortality or progression to end-stage renal disease.

Ko, et al.¹⁵ (2020) demonstrated that RTX can be safely administered in children, with infusion-related adverse events occurring in 28.1% of patients but resolving spontaneously or with symptomatic treatment.

Olfat, et al.¹⁶ (2015) found that RTX was effective and safe for cSLE-associated cytopenias, but caution is needed in patients with immune deficiencies.

DISCUSSION

Rituximab (RTX) has emerged as an effective treatment option for pediatric systemic lupus erythematosus (pSLE), particularly in cases refractory to conventional therapies. The pharmacological mechanism of RTX involves

targeting CD20-positive B cells, leading to B-cell depletion and subsequent modulation of the autoimmune response. This effect is particularly beneficial in pSLE, where B-cell hyperactivity plays a critical role in disease progression. Several studies have demonstrated the ability of RTX to significantly reduce markers of disease activity, including the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), complement levels, and anti-dsDNA antibody titers.¹⁷⁻¹⁹

The effectiveness of RTX in pediatric SLE is well-supported by multiple retrospective cohort studies. Sawhney et al. (2021) reported that RTX-treated patients showed a dramatic reduction in SLEDAI scores from 16.25 to 1.43 within six months.⁹ Similarly, Lin et al. (2024) observed a significant decrease in disease activity, with SLEDAI-2000 scores dropping from 8 to 4 over two years. Notably, both studies highlighted a sustained reduction in corticosteroid dependency, with steroid use decreasing from 100% to 33% in Sawhney et al.'s study and by 50% in Lin et al.'s study. These findings underscore the role of RTX

in reducing long-term corticosteroid exposure and its associated complications.¹⁴

Pediatric lupus nephritis remains a major indication for RTX therapy. Watson et al. (2015) found that lupus nephritis was the most common reason for RTX administration, with significant improvements in renal biomarkers such as creatinine, albumin, and urine protein-creatinine ratio within 2.5 months post-treatment.¹¹ Sawhney et al. (2021) similarly reported sustained reductions in proteinuria, demonstrating that RTX provides durable renal protection in pSLE patients with nephritis. This aligns with findings from Alsubaie et al. (2024), who highlighted the use of RTX as a second-line therapy in nephrotic syndrome and lupus nephritis, showing overall clinical improvement.^{9,13}

RTX also demonstrates efficacy in treating hematological manifestations of pSLE, particularly autoimmune cytopenias. Olfat et al. (2015) reported that 6% of cSLE patients received RTX for refractory autoimmune thrombocytopenia (AITP) or autoimmune hemolytic

anemia (AIHA), achieving a complete response in most cases within 48 days.¹⁶ However, 21% experienced flare-ups, highlighting the need for close monitoring in these patients. This suggests that while RTX is effective for hematologic complications, individualized treatment strategies may be required to maintain disease control.²⁰

In terms of safety, the reviewed studies confirm that RTX is generally well tolerated in pediatric populations. The most common adverse effects were infusion-related reactions, including mild symptoms such as fever, headache, and chest tightness, as reported by Alsubaie et al. (2024) and Ko et al. (2020).^{13,15} However, more severe reactions, such as anaphylaxis, were rare (2%-6%). Long-term safety concerns include infections, with Alexeeva et al. (2016) reporting pneumonia, neutropenia, herpes zoster, and hypogammaglobulinemia in their cohort.¹² Similarly, Olfat et al. (2015) cautioned against the use of RTX in patients with preexisting hypogammaglobulinemia due to the risk of persistent immune suppression.¹⁶

The recommended dosing regimen for RTX in pediatric SLE is typically two infusions of 375 mg/m² administered two weeks apart, as noted by Alsubaie et al. (2024).¹³ This protocol aligns with standard treatment approaches observed in clinical practice. Studies such as Lin et al. (2024) suggest that earlier administration of RTX may lead to better disease control outcomes, indicating that treatment timing is a crucial factor in optimizing efficacy.¹⁴

Short-term side effects of RTX are generally mild and include infusion-related reactions, transient lymphopenia, and mild infections. These effects are usually manageable with symptomatic treatment and do not necessitate treatment discontinuation. On the other hand, long-term adverse events, while infrequent, require careful consideration. Persistent hypogammaglobulinemia, as seen in Olfat et al.'s study, may necessitate intravenous immunoglobulin (IVIG) replacement therapy in some patients. Additionally, while no cases of mortality or end-stage renal disease were reported in the studies reviewed,

ongoing surveillance is necessary to monitor for delayed complications.¹⁶

Compared to traditional immunosuppressive regimens, RTX offers a favorable risk-benefit profile in pediatric SLE. Tambralli et al. (2015) emphasized that the incidence of hospitalized infections in RTX-treated children was comparable to historical cohorts of cSLE patients, reinforcing its safety profile.¹⁰ Watson et al. (2015) further supported RTX's role in reducing corticosteroid use, thereby mitigating the long-term risks associated with chronic steroid exposure.¹¹

Overall, RTX represents a highly effective and relatively safe option for pediatric SLE, particularly in patients with refractory disease manifestations such as nephritis and cytopenias. The available data suggest that RTX leads to significant disease control, steroid sparing, and improved renal outcomes. However, further controlled studies are needed to establish standardized protocols and long-term risk assessments. Continued pharmacovigilance is essential to ensure optimal outcomes and to minimize potential long-term

complications in pediatric SLE patients receiving RTX therapy.²¹

CONCLUSION

Rituximab is an effective and well-tolerated treatment for pediatric SLE, reducing disease activity, corticosteroid dependence, and flare-ups. While generally safe, monitoring for infusion reactions and hypogammaglobulinemia is crucial. Early administration may improve outcomes, highlighting its role in refractory pediatric SLE management.

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DAFTAR PUSTAKA

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