Am J Transl Res 2025;17(10):7602-7611
www.ajtr.org /ISSN:1943-8141/AJTR0166598

Review Article

Effects of drug administration routes on the efficacy and safety of treatments for systemic lupus erythematosus

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Received June 5, 2025; Accepted September 16, 2025; Epub October 15, 2025; Published October 30, 2025

Abstract: *Systemic lupus erythematosus (SLE)* is a highly complex autoimmune disease characterized by abnormal activation of the immune system, which attacks self-tissues and organs, leading to multi-system damage. Developing a scientifically sound treatment strategy requires comprehensive consideration of multiple factors such as drug efficacy, administration route, and patient safety. This article focuses on the impact of different administration routes on the efficacy and safety of SLE pharmacotherapy. Evidence indicates that the therapeutic efficacy and safety profiles of intravenous, subcutaneous, and oral administration vary significantly, directly affecting the rational selection of treatment plans and the overall prognosis of patients.

Keywords: Efficacy and safety, mode of administration, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE), as a chronic autoimmune disease, poses serious threats to health and greatly reduces patients' quality of life. As shown in **Figure 1**, its clinical manifestations include skin erythema, butterfly-shaped erythema on the cheeks and nose bridge, photosensitivity, recurrent painless oral or nasal ulcers, as well as systemic joint and muscle pain, all of which impose substantial physical and psychological burdens on patients [1]. Although advances have been made in the clinical treatment of SLE in recent years, numerous challenges remain. Individual differences complicate the prediction of treatment outcomes, and high-risk medications often cause obvious side effects, including infections, and hepatic or renal impairment. In the treatment of SLE, commonly used drugs include glucocorticoids and immunosuppressants [2-4]. They are effective in controlling diseases, but also have significant side effects, such as glucocorticoids-induced obesity and osteoporosis, and an increased risk of infection with immunosuppressants [5, 6]. Hence, in clinical practice, it is necessary to carefully balance efficacy and safety.

It is worth noting that while drug therapy for SLE has been extensively investigated, research on drug delivery is relatively scarce [7-9]. The choice of administration route is closely associated with drug bioavailability, and may influence patient compliance and satisfaction, ultimately affecting both therapeutic efficacy and safety [10-12].

Based on this, this article systematically reviews existing literature and clinical evidence to evaluate the efficacy and safety of different drug administration routes in SLE, aiming to provide more scientific and practical guidance for clinical management and nursing practice.

Drug therapy

Hormone therapy

Corticosteroids remain a cornerstone in the treatment of SLE due to their potent anti-inflam-

https://doi.org/10.62347/KKQM4339

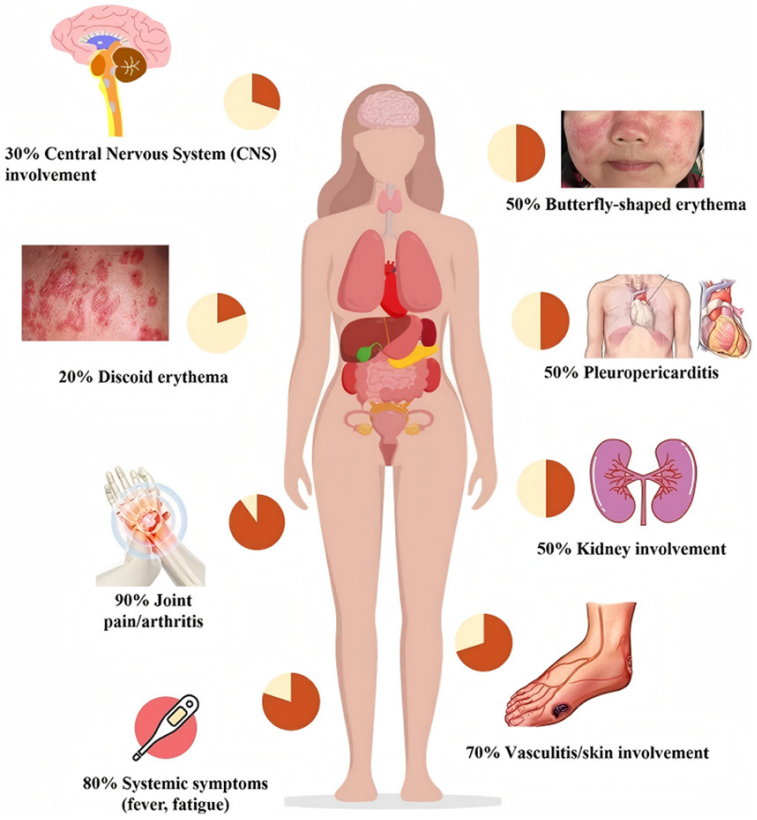

Figure 1. Clinical manifestations of SLE. Note: The patient's facial image has been obtained with their informed consent; SLE: Systemic Lupus Erythematosus; CNS: Central Nervous System.

matory and immunomodulatory effects. Their principal therapeutic mechanisms include suppression of the inflammatory response, modulation of immune activity, and regulation of leukocyte distribution and function [13, 14]. At the genomic level, the cytosolic glucocorticoid receptor complex bindis to DNA and modulates transcription of pro-inflammatory genes, accounting for both the therapeutic efficacy and many of the metabolic adverse effects [15]. Hydrocortisone exerts anti-inflammatory and anti-allergic effects by inhibiting macrophage activity, lowering parathyroid hormone levels, reducing platelet antibody production, and preventing antibody binding to platelet membranes, thereby reducing platelet destruction [16, 17]. Dexamethasone, another commonly used therapeutic drug for SLE, suppresses immune complex deposition, inhibits antiplatelet antibody production, and promotes platelet recovery; however, prolonged administration may induce drug resistance and reduce efficacy [18, 19]. This resistance is often associated with downregulation of glucocorticoid receptor expression and activation of pro-inflammatory pathways, such as mitogen-activated protein kinase (MAPK), which counteracts glucocorticoid activity [20]. These hormonal drugs are crucial in managing SLE by targeting inflammation and modulating immune response, thereby alleviating symptoms and improving overall patient outcomes [21, 22], as summarized in **Table 1**.

Effects of different administration routes on the efficacy of hormonal drugs: Hormonal drugs play a key role in the treatment of SLE owing to their ability to control inflammation and modulate immune activity. They can be administered orally (PO), intravenously (IV), or subcutaneously (SC), and each route has unique safety and efficacy characteristics, which directly influence patient outcomes and treatment experience [23-26]. For instance, IV pulse therapy (e.g., methylprednisolone) provides rapid immunosuppression, making it crucial for managing severe flares like nephritis, but is associated with acute side effects, including hypertension and hyperglycemia [27]. In contrast, oral regimens provide sustained disease control but pose a greater risk of cumulative toxicity like osteoporosis [28]. The choice of administration route is influenced by various factors, including patient- related variables (e.g., age, comorbidities, compliance, gastrointestinal function, skin condition), drug-related characteristics (molecular structure, physicochemical properties, pharmacokinetics, dosage form), and socio-economic factors. Furthermore, the selection must align with therapeutic goals, and balance safety and potency to optimize outcomes, as summarized in **Table 2** [29, 30].

Influence of patient factors on the efficacy of hormonal drug: Individual patient characteristics significantly influence both the selection

Table 1. Classification and therapeutic mechanism of hormonal drugs

Hormonal drugs	Mechanism of action
Cortisone	Inhibits the release of inflammatory mediators and reduces the activity of immune cells
Prednisone	Reduction of inflammatory factor expression through inhibition of the NF-κB pathway
Prednisolone	Similar to prednisone, but with longer half-life and longer lasting effects
Dexamethasone	Powerful anti-inflammatory and immunosuppressive effects
Methylprednisolone	Used in acute exacerbations for rapid control of the disease
Betamethasone	Efficient immunosuppression for critically ill patients
Triamcinolone acetonide	Reduced risk of systemic side effects through local effects

NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells.

Table 2. Dosage form differences and their effects on safety and efficacy

Mode of administration	Safety	Potency
Oral (PO)	Facilitates long-term management, but may lead to increased gastrointestinal side effects	Suitable for long-term control, absorption affected by food
Intravenous (IV)	Directly enters the bloodstream for immediate effect, reducing gastrointestinal side effects	Ideal for acute exacerbations and rapid control
Subcutaneous Injection (SC)	Reduced gastrointestinal side effects, but injection site reactions may occur	Stable absorption for situations where oral intake is not possible or continuous administration is required

PO: Per Os (by mouth); IV: Intravenous; SC: Subcutaneous.

Table 3. Common modes of administration of different immunosuppressive drugs

Immunosuppressant	Oral (PO)	Intravenous (IV)	Subcutaneous (SC)
Cyclophosphamide (CTX)	√	√	
Matemacrolate (MMF)	√		
Azathioprine (chemistry)	√		
Cyclosporine (CsA)	√	√	
Tacrolimus (FK506)	√	√	
Methotrexate (MTX)	√	√	√
Leflunomide (LEF)	√		

CTX: Cyclophosphamide; MMF: Mycophenolate Mofetil; CsA: Cyclosporine A; FK506: Tacrolimus; MTX: Methotrexate; LEF: Leflunomide; PO: Per Os (by mouth); IV: Intravenous; SC: Subcutaneous.

and dosing of hormonal drugs, as well as their therapeutic efficacy and safety. Key considerations include age, sex, and comorbidities.

Pediatric patients may respond differently to hormonal treatment due to their rapid metabolic rate and ongoing growth. Prolonged exposure may impair linear growth and skeletal maturation, potentially leading to height retardation. Annual monitoring of growth velocity and bone age is recommended, and growth hormone therapy can be considered in cases of severe growth retardation. Although gender has limited impact on corticosteroid pharmacodynamics, attention should be paid to the risk of osteoporosis in female patients, especially postmenopausal women [31-33]. Baseline dual-energy X-ray absorptiometry (DXA) is advised, along with calcium and vitamin D supplementation; bisphosphonates should be considered if long-term therapy is required [34, 35]. In patients with diabetes mellitus or impaired glucose tolerance, corticosteroids may exacerbate hyperglycemia. Regular glucose monitoring and close collaboration with an endocrinologist are essential, as insulin therapy is often required to manage steroid-induced hyperglycemia [36].

Immunosuppressants

Effects of different administration routes on the efficacy of immunosuppressants: Immunosuppressants can be administered through various routes, each with distinctive advantages and limitations [37-39], as summarized in **Table 3**. Oral administration is the most common and convenient approach for long-term

immunosuppression. However, agents such as mycophenolate mofetil can cause significant gastrointestinal distress, and their absorption can be variable, sometimes requiring therapeutic drug monitoring to ensure efficacy and minimize toxicity [40]. IV administration is preferred when rapid disease control is required or when patients cannot tolerant oral medications. Direct entry into the systemic circulation allows for swift therapeutic action, but repeated infusions may be necessary to maintain adequate therapeutic levels [41]. SC administration offers a practical alternative, combining convenient long-term dosing with avoidance of the gastrointestinal irritation [42]. For drugs like methotrexate, SC injection ensures more consistent and complete bioavailability compared to oral administration, which is particularly advantageous in patients with poor response or gastrointestinal side effects [43].

Effects of patient factors on the efficacy of immunosuppressants: When selecting an immunosuppressive regimen, patient-specific factors such as renal and hepatic function are critical. Renal impairment may require dose adjustments or avoidance of certain agents to reduce toxicity, while hepatic dysfunction can affect drug metabolism and clearance, necessitating close monitoring and individualized dosing. For example, cyclophosphamide is primarily excreted by the kidneys and should be dose-reduced in patients with chronic kidney disease (CKD), while azathioprine metabolism is influenced by liver function and thiopurine S-methyltransferase (TPMT) activity, requiring TPMT genotyping or phenotyping prior to initiation to avoid severe myelosuppression [44, 45]. Additionally, reviewing a patient's prior medication history is essential for evaluating drug tolerance and potential drug-drug interactions, enabling a tailored treatment plan [46].

Anti-malarial drugs

Effects of different administration routes on anti-malarial drugs: Hydroxychloroquine, the most commonly used anti-malarial agent in SLE, is generally available as an oral tablet. Its dosage and release characteristics may vary by manufacturer, and generic substitution can lead to differences in bioavailability. To maintain stable blood concentrations and consistent therapeutic effect, particularly given hydroxychloroquine's long half-life and narrow therapeutic index, patients are advised to remain on the same product brand whenever possible [47]. They should follow medical instructions carefully and avoid unapproved changes in dose or brand to prevent treatment interruption or fluctuating efficacy [48].

Effects of patient factors on anti-malarial drug efficacy: Renal and hepatic function: Hydroxychloroquine is primarily excreted through the kidneys and metabolized by the liver; therefore, caution is warranted in patients with renal or hepatic insufficiency, and dosage adjustments may be necessary [49]. In cases of severe impairment, alternative therapies should be considered, as drug accumulation significantly increases the risk of irreversible retinal toxicity [50].

Ophthalmic monitoring: Long-term hydroxychloroquine therapy may induce ocular adverse effects, particularly retinopathy. Regular ophthalmic examinations are recommended throughout treatment.

Other comorbidities: Patients with SLE may have a variety of comorbidities that requires consideration when prescribing hydroxychloroquine. For instance, its use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency remains controversial due to a small but potential risk of hemolysis; and baseline screening may be appropriate in high-prevalence populations [51].

Biological agents

Effects of different administration routes on the efficacy of biological agents: Biological agents, such as rituximab, play an important role in the treatment of SLE. They are primarily administrated by two routes (IV and SC), each with distinct clinical considerations. Intravenous infusion rapidly increase plasma drug concentration, achieving rapid therapeutic action. This route generally requires administration in a professional medical facility, where medical staff can promptly manage related adverse events (e.g., cytokine release syndrome) and ensure patient safety. Pharmacokinetically, IV infusion provides complete bioavailability and allows precise control of the infusion rate, which is critical for minimizing infusion-related reactions. Therefore, IV administration is more suitable for patients with urgent treatment needs.

Subcutaneous injection offers more stable plasma drug concentrations and allows for longer dosing intervals. Its principal advantage is convenience: patients can complete injections at home without frequent visits to medical institutions, greatly improving patient compliance and reducing the number of visits. Therefore, SC administration is an ideal choice for long-term disease management, especially for patients requiring prolonged therapy.

Effects of patient factors on the efficacy of biological agents: When prescribing biological agents, clinicians should carefully consider individual patient characteristics, including disease activity and severity, lifestyle, and quality of life, to ensure an optimal therapeutic strategy. Tailoring treatment to these factors helps maximize efficacy, improve adherence, and minimize unnecessary exposure to complex regimens.

Influence of routes of administration on drug safety and efficacy

Comparison of absorption, distribution, metabolism, and excretion (ADME) among routes

In pharmacology, ADME of drugs are critical determinants of their efficacy and safety. Different administration routes profoundly influence the ADME profile, thereby affecting therapeutic response and the risk of adverse effects [52]. This chapter compares the ADME characteristics of three common routes of administration.

The drug distribution process mainly involves the transmission of drugs in the body through blood circulation and their affinity with tissues. IV administration bypasses absorption, allowing drugs to enter the bloodstream directly and distribute rapidly throughout the body. In contrast, PO and SC administrations require an absorption process before reaching systemic circulation. Lipid solubility, molecular size, and plasma protein binding capacity all influence drug distribution in the body. Most drug metabolism occurs in the liver, although the intestine and kidneys also contribute. PO drugs are subjected to first-pass metabolism in the liver, which can markedly reduce bioavailability. IV and SC routes can bypass first-pass metabolism, allowing a greater proportion of the active drug to remain in circulation. Excretion is mainly completed through urine and other means, depending on the characteristics of the drug itself.

Influence of administration route on drug effectiveness

Administration route affects the safety and efficacy of drugs by altering ADME characteristics. These processes collectively determine key parameters such as bioavailability, therapeutic effect, and toxicity. IV administration can rapidly deliver drugs into systemic circulation, which is essential in emergencies that require immediate intervention. However, this route can cause high plasma concentration within a short time, increasing the risk of toxicity and requiring close monitoring by medical personnel. PO administration is more convenient, and patients can self-administer therapy at home. However, variability of gastrointestinal absorption and the hepatic first-pass effect can lead to inconsistent bioavailability, thereby influencing overall efficacy. In addition, the administration route influences drug distribution, potentially exposing non-target tissues and increasing adverse effects. However, targeted delivery strategies, such as local delivery can minimize off-target exposure, enhance efficacy, and improve safety, offering new therapeutic prospects for patients [53].

Influence of administration route on drug safety

Administration route has a significant impact on drug safety. IV delivery ensures nearly complete bioavailability and allows drugs to reach therapeutic concentrations quickly. However, direct entry into the bloodstream may trigger allergic reactions, ranging from rash and pruritus to, in severe cases, life-threatening anaphylaxis. IV therapy may also irritate local blood vessels, potentially complicating subsequent treatment. Oral administration is convenient but may irritate the gastrointestinal mucosa, causing adverse reactions such as nausea, abdominal discomfort, or diarrhea. SC or intramuscular (IM) injection can cause localized reactions such as pain and redness, affecting the patient's daily activities.

Administration routes influence drug metabolism and thereby affect drug safety. Oral medication undergoes hepatic metabolism, which

may either enhance drug toxicity or decrease efficacy. Pharmacokinetic and pharmacodynamic studies conducted before and during clinical trials can accurately evaluate the effects of different administration routes on drug metabolism, providing scientific basis for rational clinical applications. At the same time, the choice of administration method also needs to consider patient compliance. Oral administration typically enhances compliance owing to its convenience, whereas frequent injections may lead to treatment fatigue or resistance, potentially compromising outcomes. Selecting an appropriate route of administration is therefore critical for optimizing both safety and therapeutic success.

During drug development and clinical application, it is essential to thoroughly evaluate drug characteristics and mechanisms of action, while also considering disease characteristics and individual patient needs. In addition, continuous development of new drug delivery technologies and systems are expected to enhance the precision and controllability of drug action, further improving therapeutic safety and efficacy.

Effects of population differences on drug exposure

Administration route directly influences drug safety and tolerability. IV injection provides rapid drug activation but may cause allergic reactions or irritate blood vessels. Oral administration is convenient but can cause gastrointestinal discomfort such as nausea and vomiting. Subcutaneous or intramuscular injection may lead to pain, redness, and swelling at the injection site. Different administration routes can also alter drug metabolism, thereby affecting drug toxicity and efficacy. Oral drugs undergo hepatic metabolism and are prone to drug-drug interactions. In addition, patient compliance is another key factor: oral administration is convenient with improved patient compliance, while frequent injections can reduce adherence [54].

Selecting an appropriate administration route is essential to ensure both drug efficacy and safety. This requires a comprehensive understanding of drug characteristics, the specific needs of the target population, and the stage of disease. With ongoing advances in drug delivery systems, emerging technologies continue to enhance the precision, safety, and overall effectiveness of drugs [55].

Racial differences are an important consideration in evaluating drug efficacy and safety. Genetic polymorphisms, as the main biological basis of ethnic variability, play a key role in drug metabolism [56]. For instance, clinical studies on certain cardiovascular medications have shown significant racial differences in both therapeutic efficacy and the incidence of adverse effects. These findings highlight the need for clinicians to consider not only the patient's disease status but also their ethnic background when formulating individualized treatment plans to ensure treatment effectiveness and patient safety.

Lifestyle factors, such as smoking and diet can influence drug metabolism. For example, smoking induces several drug-metabolizing enzymes, accelerating drug clearance and reducing plasma concentration and therapeutic efficacy. Polycyclic aromatic hydrocarbons in tobacco smoke are potent inducers of CYP1A2 and other enzymes, which can significantly reduce the bioavailability and efficacy of drugs metabolized by these pathways, such as clozapine and theophylline [57]. A healthy diet and moderate exercise can improve overall metabolic function and support effective drug therapy. Pharmacologic regimens for patients with multiple diseases require a comprehensive consideration of the various disease states and drug-drug interactions. Comorbidities such as hepatic and renal impairment can alter drug metabolism and excretion, increasing the risk of toxic reactions.

Patient adherence and route of drug administration

Patient compliance, i.e., the extent to which patients take medications as prescribed, is a critical determinant of drug efficacy and treatment success. Different administration routes substantially influence adherence, encompassing not only convenience and comfort but also the patient's perception and acceptance of the treatment process [58]. Given the chronic nature of SLE, long-term pharmacotherapy is often required. The burden of frequent dosing, such as multiple daily oral tablets or repeated injections, can lead to intentional non-adherence. This is particularly evident in regimens

requiring tapering corticosteroids, where self-discontinuation due to distressing side effects is a common challenge. Strategies to enhance adherence include improving the convenience and tolerability of administration, strengthening patient education to foster understanding and acceptance of therapy, and developing novel delivery systems (e.g., controlled-release formulations, wearable delivery devices) to reduce dosing frequency and simplify treatment.

Conclusion

In SLE treatment, the route of administration significantly affects treatment efficacy and safety. Intravenous and subcutaneous routes influence patient response and tolerance, underscoring the need for tailored treatment plans. Selecting an appropriate administration route based on patient characteristics and drug properties is essential for optimizing clinical outcomes. Future research should focus on advancing drug delivery methods for SLE towards more refined and personalized approaches. Such progress will not only enhance the intrinsic value of pharmacologic agents but also serve as a critical step in improving the quality of life and treatment success in SLE patients.

Disclosure of conflict of interest

None.

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