International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 6 | Issue: 6 | Nov – Dec 2025 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v6i6.20

Transitioning Steroid-Dependent Erythema Nodosum Leprosum to Methotrexate-Based Management: A Literature Review

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ABSTRACT

Erythema nodosum leprosum (ENL) is a devastating immune system disorder that affects up to 50% of lepromatous leprosy patients. It causes recurring painful nodules and body-wide inflammation. Current treatment focuses mainly on long-term glucocorticoid medication, but 82% of patients become reliant on steroids, causing metabolic abnormalities, osteoporosis, infections, and lower quality of life. Thalidomide works, but its teratogenicity, legal constraints, and side effects make it difficult to obtain worldwide. Due to the need for effective steroid-sparing alternatives, methotrexate (MTX) is being investigated. Neutrophil activation, neutrophil extracellular trap formation, and cytokine networks are key mechanisms in ENL pathogenesis, and MTX's adenosine-mediated anti-inflammatory activities directly affect them. MTX controls the disease and makes glucocorticoids lowerable, according to recent clinical trials like the MaPs in ENL experiment and a French multicenter investigation. In fact, 54–61% of patients achieved steroid-sparing results. As an alternative to standard techniques, low-dose weekly MTX is safe, cost-effective, widely available, and monitored. This review draws on current ENL pathophysiology, rigorously evaluates steroid dependency, analyzes the mechanistic justification and clinical evidence for MTX-based treatment, and provides a pragmatic framework for switching patients from glucocorticoids to MTX. This promising treatment for one of leprosy's most difficult sequelae needs further study to define effective dose regimes, discover predictive biomarkers, and evaluate long-term outcomes.

Keywords: erythema nodosum leprosum; methotrexate; steroid therapy

BACKGROUND

Erythema nodosum leprosum (ENL), or Type 2 lepra reaction, is one of the most difficult immunological problems in lepromatous and borderline lepromatous leprosy. It affects up to 50% of people with lepromatous leprosy and about 5–10% of people with borderline lepromatous disease [1,2,3]. This serious inflammatory disorder affects multiple systems and causes sudden outbreaks of painful, short-lived erythematous nodules. It can also cause systemic symptoms like fever, arthralgia, neuritis, and organ involvement that could be life-threatening [2,4]. Because ENL is a long-lasting and recurring condition, patients need to take immunosuppressive drugs for a long time, often for months or years. This has a big effect on their health, death rate, and quality of life [1,15]. Managing steroid-dependent ENL is still a big problem in modern leprosy care. New ways must be found to reduce the harmful effects of glucocorticoids while keeping the disease under control.

PATHOPHYSIOLOGICAL OF ENL

Recent transcriptomic and immunological studies have significantly altered our comprehension of ENL pathogenesis, which identify neutrophils as primary orchestrators rather than passive participants in the inflammatory process [7,8]. Innovative whole blood transcriptomic analysis has revealed significant enhancement of neutrophil activation pathways during ENL episodes, particularly highlighting neutrophil extracellular trap (NET) formation as a principal pathogenic mechanism [7]. The presence of elevated DNA-histone and DNA-myeloperoxidase complexes in the sera of ENL patients, along with the increased spontaneous formation of neutrophil extracellular traps (NETs) by peripheral blood neutrophils, confirms NETosis as a crucial element of ENL pathophysiology [6,8].

The immune complex-mediated aspect of ENL entails the deposition of antibody-antigen complexes that activate neutrophils via Fc gamma receptor IIA (FcγRIIA) engagement, initiating a series of inflammatory responses such as degranulation, reactive oxygen species production, and cytokine release [5,8,9]. This mechanism is similar to what happens in other immune complex-mediated diseases, which means that there may be ways to treat these diseases by targeting neutrophil activation pathways [13,14]. Recent studies have identified CD177 as a potential systemic biomarker for ENL severity, with increased serum levels correlating with disease intensity [12].

The pro-inflammatory cytokine environment in ENL is marked by significant increases in tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), resulting in a self-sustaining inflammatory condition [5,10,11]. These cytokines work together to boost the recruitment of immune cells, activate endothelial cells, and cause tissue damage through many different pathways that are all linked together. TNF-α, primarily released by activated macrophages and T cells, stimulates the production of downstream cytokines and enhances vascular permeability, thereby enabling leukocyte extravasation into affected tissues [63]. IL-6, via classical and trans-signaling pathways, orchestrates the acute phase response and facilitates B-cell differentiation and T-cell activation, thereby contributing to the systemic manifestations associated with severe ENL [11].

Recent studies have clarified the pivotal function of NF-κB and STAT3 signaling in maintaining this hyperinflammatory condition, with synergistic interactions between these transcription factors promoting continuous cytokine production, even in the absence of ongoing antigenic stimulation [10,42]. This mechanistic understanding offers essential justification for therapeutic strategies aimed at these pathways, such as methotrexate, which exhibits pleiotropic effects on various nodes within these inflammatory networks [31,32].

ENL presents with varying degrees of severity, ranging from acute self-limited episodes to chronic unremitting inflammation necessitating ongoing immunosuppression [1,4]. The categorization of ENL into acute (lasting less than 24 weeks), recurrent (with second or subsequent episodes occurring 28-84 days after treatment cessation), and chronic (lasting more than 24 weeks with treatment-free intervals of 27 days or less) has substantial therapeutic ramifications [1,4]. About 95% of patients who need advanced therapies have chronic or recurring patterns, and in specialized referral centers, the median length of the disease is more than 49 months [1].

Severe ENL can evolve into vasculonecrotic variants marked by ulceration, necrosis, and involvement of multiple organs, including glomerulonephritis, myositis, iridocyclitis, and orchitis [16,59].

Recent case series have reported infrequent yet catastrophic complications, including palatal perforation in relapsed lepromatous leprosy with fulminant necrotic ENL [59], highlighting the urgent necessity for efficient disease control strategies that reduce both disease-associated and treatment-associated morbidity.

THE BURDEN OF GLUCOCORTICOID DEPENDENCY

Even though prednisolone is still the first-line treatment for ENL, steroid dependency is almost always a result of long-term and recurring disease [19,23]. Retrospective analyses indicate that 16% of patients are already steroid-dependent upon presentation, while a concerning 82% develop dependency during the treatment course [19]. This dependency is shown by the fact that patients can not lower their prednisolone dose below 10 mg a day without getting new lesions or making their current inflammation worse. This keeps patients in a cycle of high-dose glucocorticoid exposure [19,23]. The temporal dynamics of ENL management exhibit particularly alarming trends, as Type 2 reactions necessitate considerably prolonged treatment durations in contrast to Type 1 reactions [1,47]. Patients who are exposed to glucocorticoids at doses higher than 20–40 mg per day for a long time are at a much higher risk of experiencing all the negative effects that come with corticosteroids [19,22].

Systematic evaluation of long-term glucocorticoid therapy in leprosy reactions has documented adverse effects in 60-80% of patients, with the burden disproportionately affecting those with Type 2 reactions due to extended treatment duration [19,20]. The multisystem toxicity of chronic glucocorticoid exposure encompasses metabolic derangements, including steroid-induced diabetes mellitus (observed in patients receiving more than 20 mg daily), dyslipidemia, and hypertension [22]; musculoskeletal complications, notably glucocorticoid-induced osteoporosis affecting up to 40% of long-term users with accelerated trabecular bone loss occurring within the first 6-12 months [21], avascular necrosis, and steroid myopathy; infectious complications resulting from dose-dependent (greater than 10 mg daily) and cumulative dose-dependent (greater than 700 mg total) immunosuppression [22]; dermatological manifestations including cushingoid features, striae, and impaired wound healing; and neuropsychiatric effects ranging from insomnia and mood disorders to frank psychosis and cognitive dysfunction [22].

Recent systematic reviews underscore that adverse effects are strongly associated with daily dosage, cumulative exposure, and concomitant medications, indicating that patients receiving prednisolone exceeding 40 mg daily or with elevated cumulative doses face significantly higher complication rates [19,22]. The mortality rate linked to ENL, observed at alarming levels in Ethiopian cohorts, signifies both the severity of the disease and complications arising from treatment [15], underscoring the pressing necessity for safer therapeutic options.

The economic burden of prolonged ENL treatment transcends direct medical expenses, resulting in considerable productivity losses, as affected individuals experience prolonged disability [17,61]. Family members of ENL patients endure significant economic distress, as the household expenses associated with ENL reactions exert considerable financial pressure [17]. This socioeconomic aspect heightens the necessity for formulating effective, economical, and well-accepted long-term management strategies [18].

LIMITATIONS OF CURRENT THERAPEUTIC OPTIONS

Thalidomide, despite showing remarkable effectiveness in ENL with response rates exceeding 80% in steroid-resistant cases, encounters significant challenges in global implementation [23,24,25]. Because it is so well-known for causing birth defects, strict programs to prevent pregnancy are needed, which means that only women who are not pregnant can use it, and only specialized centers with strong monitoring systems can get it [26,27]. Regulatory obstacles have led to thalidomide's approval solely in specific endemic nations, such as India and Brazil, thereby denying extensive populations access to this highly efficacious agent [26,27].

In addition to teratogenicity, thalidomide poses considerable risks of peripheral neuropathy alongside dose-dependent bradycardia, sedation, and thromboembolic occurrences [23,66,67]. Cost factors make it even harder to get to leprosy in places where it is still common [27]. These various limitations highlight the urgent necessity for alternative steroid-sparing agents that offer similar effectiveness while providing enhanced safety and accessibility.

Clofazimine, although it has anti-inflammatory properties and is often used as a steroid-sparing agent, is not as effective as thalidomide. For example, the rates of non-recurrence are only 66% for clofazimine and 80% for thalidomide combination therapy [28,50]. Its gradual onset of action (usually 4–6 weeks) makes it less useful for treating acute severe ENL, and the skin pigmentation that comes with it, while reversible, is a cosmetic issue that can make patients less likely to accept it [28]. Various immunosuppressive agents, such as azathioprine, cyclosporine, and pentoxifylline, have been investigated with inconsistent outcomes; however, none have gained widespread acceptance owing to insufficient efficacy data, particular contraindications, or adverse safety profiles [29,30].

EMERGING EVIDENCE OF METHOTREXATE

Methotrexate (MTX) stands out as a potent therapeutic choice for ENL due to its diverse anti-inflammatory mechanisms that specifically target critical pathogenic pathways [31,32]. Originally designed as an antifolate dihydrofolate reductase inhibitor for cancer chemotherapy, low-dose weekly MTX's immunomodulatory effects work through very different pathways, mainly through adenosine signaling [33].

MTX polyglutamates inhibit the enzyme aminoimidazole carboxamide ribonucleotide transformylase (ATIC), which causes AICAR to build up inside cells. This then stops adenosine deaminase and AMP deaminase, which raises the levels of adenosine outside of cells [32,33]. Adenosine, through A2A and A3 receptors on immune cells, has strong anti-inflammatory effects. These include stopping neutrophil activation and NET formation, lowering the production of TNF-α, IL-6, and IL-1β by macrophages and monocytes, stopping T-cell proliferation and cytokine secretion, and downregulating NF-κB translocation, which stops the inflammatory amplification loop [31,32,34].

These mechanistic actions directly oppose the pathogenic processes that cause ENL, especially the inflammation and cytokine storm caused by neutrophils that are typical of severe disease [7,8]. Other ways that MTX works include stopping transmethylation reactions that affect the stability of cytokine mRNA, changing JAK-STAT signaling pathways, and stopping the production of reactive oxygen species [31,34,35].

The use of MTX in leprosy reactions has progressed from isolated case reports to comprehensive clinical studies, culminating in the seminal MaPs in ENL (Methotrexate and Prednisolone studies in Erythema Nodosum Leprosum) trial, the largest randomized controlled trial ever conducted for ENL treatment [36]. This international multicenter double-blind RCT, with 414 participants from six countries (Bangladesh, Brazil, Ethiopia, India, Indonesia, and Nepal), tests how well MTX works as a steroid-sparing agent for both acute and chronic/recurrent ENL [36].

The MaPs protocol uses weight-based MTX dosing (15 mg per week for patients under 60 kg and 20 mg per week for patients 60 kg or more) for 48 weeks, along with prednisolone, which is slowly reduced to zero over 20 weeks [36]. This design directly tackles the important question of whether MTX can help lower steroids over time while still keeping the disease under control. Initial findings from this ongoing trial indicate potential steroid-sparing effects, although results are eagerly anticipated [36]. A French multicenter retrospective study provides supplementary evidence, indicating that MTX (7.5-20 mg weekly) elicited a favorable response in 61.5% of patients with refractory leprosy reactions, encompassing both ENL and reversal reactions [37]. This study importantly recorded successful glucocorticoid-sparing in 54.5% of patients, with complete withdrawal achievable in certain instances [37].

The finding that early introduction of MTX during leprosy reactions resulted in enhanced therapeutic responses indicates a potential advantage of proactive therapy over rescue therapy; however, the 42% relapse rate following MTX discontinuation underscores the necessity for an extended treatment duration [37].

A randomized controlled pilot study from Bangladesh comparing MTX plus prednisolone versus prednisolone monotherapy in ENL demonstrated superior safety profiles and effectiveness with combination therapy, including better nodule resolution, though the small sample size and short follow-up period limited conclusions regarding steroid-sparing effects [38]. Case series from resistant ENL have historically documented successful MTX responses in patients unresponsive to both prednisolone and thalidomide, thereby establishing proof-of-concept for MTX efficacy in the most challenging cases [38,39,40].

MTX at low weekly doses (15–20 mg) has a well-known safety record based on a lot of rheumatological research, and its side effects are easy to predict and deal with [43,44,45]. Gastrointestinal symptoms, especially nausea (which affects up to 35% of patients), are the most common side effects. Taking folic acid at the same time (5 mg daily) can help with nausea and prevent hematological toxicity without lowering the effectiveness of the treatment [43,44]. Less common but still important side effects that need to be watched for are hepatotoxicity (usually mild transaminase elevations), myelosuppression (usually dose-dependent and reversible), and pulmonary toxicity (rare but serious) [44,46].

It is important to note that there are clear contraindications to MTX use that can be easily found through a baseline evaluation [44,52]. The established monitoring protocols, which include a complete blood count and tests of liver and kidney function every 4 to 8 weeks at first and then every 12 weeks once the patient is stable, create a strong safety net [44,45]. This advanced comprehension of MTX pharmacology and toxicity stands in favorable contrast to thalidomide's unpredictable and frequently irreversible adverse effects [23,26].

COMPARATIVE ADVANTAGES OF METHOTREXATE-BASED MANAGEMENT

MTX is one of the most affordable immunosuppressive drugs in the world. Generic versions are easy to find and cost much less than thalidomide or biologic therapies [51]. The WHO List of Essential Medicines includes MTX because it is already used to treat many different conditions and is available even in places where leprosy is still common [51]. MTX is a good choice for health systems that have a lot of leprosy because it is cheap and could greatly lower the number of complications and healthcare costs related to glucocorticoids [17,52].

In contrast to thalidomide, which requires specialized pregnancy prevention programs and limited distribution networks, the administration and monitoring of MTX can be integrated into current primary and secondary healthcare systems [26,27,44]. The monitoring requirements are in line with standard protocols for managing chronic diseases. This makes it easier to include leprosy care in general medical practice instead of needing specialized knowledge [44,45]. This scalability is a big plus for programmatic implementation, especially in decentralized health systems [54].

MTX-based management can greatly improve a patient's quality of life by allowing for the reduction or elimination of high-dose glucocorticoid therapy while keeping the disease under control [18,37]. Steering clear of cushingoid traits, metabolic problems, and mental health issues that come with long-term glucocorticoid use can greatly improve social functioning and emotional health, two very important things to think about in a disease that already has a lot of stigma [17,18]. Moreover, maintaining bone health and preventing avascular necrosis may diminish long-term disability, which is particularly significant considering the youth of many ENL patients [21,61].

TRANSITIONING TO MTX-BASED MANAGEMENT

The ideal candidates for transitioning to MTX are patients with chronic or recurrent ENL necessitating prednisolone doses exceeding 10 mg daily for extended durations (typically beyond 12 weeks), those experiencing considerable glucocorticoid-related adverse effects, patients with steroid-refractory disease requiring increasing doses, and individuals in circumstances where thalidomide access is restricted or contraindicated [19,37]. On the other hand, relative contraindications include severe renal insufficiency (estimated glomerular filtration rate below 30 mL/min/1.73m^2), active hepatic disease or significant hepatic impairment, current alcohol use disorder, pregnancy or inadequate contraception in women of childbearing potential, significant baseline cytopenias, and concurrent severe infections [44].

Risk stratification must include the evaluation of ENL severity through validated instruments like the ENLIST ENL Severity Scale (EESS) [4], the assessment of organ involvement (especially neuritis, nephritis, and ocular complications), baseline laboratory parameters (complete blood count, hepatic and renal function, inflammatory markers), and the analysis of glucocorticoid exposure burden and associated complications [19,22].

A systematic method for starting MTX strikes a balance between monitoring safety and therapeutic effectiveness [36,37,44]. The suggested protocol includes a full history and physical exam, a complete blood count with differential, a comprehensive metabolic panel that checks liver and kidney function, a chest X-ray to rule out subclinical pulmonary disease, and a pregnancy test for women who could become pregnant [44]. The first dose of MTX follows standard guidelines: for patients under 60 kg, 10–15 mg orally once a week; for patients 60 kg or more, 15–20 mg orally once a week; and for all patients, 5 mg of folic acid daily to reduce side effects [36,37,44].

During the transition phase, prednisolone tapering should be done carefully, usually starting 4 to 6 weeks after starting MTX to give the drug time to work [37,53]. A proposed tapering schedule decreases

prednisolone by 5 mg every 2-4 weeks while the disease remains controlled, transitioning to a slower reduction of 2.5 mg increments as doses near physiological replacement levels (approximately 7.5 mg), necessitating vigilant monitoring at each decrement for indications of disease exacerbation [36,47,53].

Systematic monitoring protocols make sure that MTX-related toxicity is found early [44,45]. In the first three months, monthly complete blood counts, liver function tests, and renal function tests keep a close eye on things during the time when the risk is highest [44]. After that, monitoring can happen every 8 to 12 weeks once the patient is stable. New symptoms, especially cough, dyspnea, fever, or progressive fatigue, should always be watched for, as they could mean pulmonary or hepatic toxicity [44,46]. Management of prevalent adverse effects entails dose modification for enduring nausea despite folic acid supplementation, a temporary cessation of medication for concurrent infections, and immediate discontinuation with specialist consultation if substantial hepatic, hematological, or pulmonary toxicity arises [44,52].

Treatment success includes many things: clinical disease control (no new ENL lesions, resolution of systemic symptoms, and stability or improvement of organ involvement), steroid reduction (getting prednisolone doses below 10 mg daily or stopping completely), no serious side effects, and improvement in quality of life measures [37,53]. The ideal duration of MTX therapy necessitates further examination; however, evidence from leprosy reactions and rheumatological conditions indicates that treatment should be sustained for 12-24 months post-stable disease control before initiating a gradual taper, with preparedness to resume if relapse occurs [37,45,53]. The elevated relapse rate (42%) noted following the cessation of MTX in the French study indicates that extended treatment may be required for numerous patients [37].

FUTURE RESEARCH DIRECTIONS

Essential inquiries necessitating conclusive responses via forthcoming trials encompass the establishment of optimal MTX dosing strategies (fixed versus weight-based, conventional versus elevated doses), the identification of the ideal therapy duration and tapering protocols to mitigate relapse, the comparative effectiveness against thalidomide in direct trials, and the assessment of combinatorial approaches with other immunomodulatory agents beyond glucocorticoids [36,37,45].

The future of managing ENL lies in precision medicine that uses biomarkers to predict how well a treatment will work and how to best use it [7,12,35]. Priority areas encompass the validation of neutrophil activation markers (CD177, calprotectin, NET components) as biomarkers for severity and treatment response [7,12], the identification of pharmacogenomic predictors of MTX efficacy and toxicity [35], the characterization of the transcriptomic signature that differentiates MTX responders from non-responders [7], and the development of point-of-care assays for real-time treatment optimization. Recent transcriptomic studies identifying NLRP6 and IL5RA as potential therapeutic targets in thalidomide treatment indicate that analogous methodologies may clarify MTX-specific mechanisms [42].

Emerging mechanistic insights into ENL pathogenesis suggest innovative therapeutic strategies warranting investigation, including selective targeting of FcγRIIA to interrupt immune complex-mediated neutrophil activation [8,9], inhibition of NET formation through peptidylarginine deiminase 4 (PAD4) antagonists [6,14], modulation of NLRP6 inflammasome signaling [42], biologic agents targeting key cytokines (TNF-α, IL-6, IL-1β) [10,11,63], and combination immunometabolic approaches addressing the metabolic reprogramming characteristic of chronic inflammation [65,68].

IMPLEMENTATION CONSIDERATIONS

To successfully translate MTX-based ENL management from controlled trials to everyday practice, it is important to focus on how to fit it into the existing health infrastructure [54,57]. This includes creating clinical guidelines and treatment algorithms that can be used in different resource settings [27,54], training programs for primary care providers and dermatologists on how to prescribe and monitor MTX [44], setting up laboratory networks that make sure people can get the tests they need [44], and making patient education materials that explain how to take the medication, how to recognize side effects, and how important it is to stick to the treatment [18].

Considering the limited experience with MTX in ENL relative to rheumatological indications, the creation of prospective registries that record real-world effectiveness, safety, and long-term outcomes would yield essential data to enhance clinical practice [52,53]. These registries ought to encompass comprehensive data regarding dosing protocols, concomitant medications, adverse events, and patient-reported outcomes across various geographical and demographic contexts [54,70].

The success of any ENL treatment strategy goes beyond just how well the drugs work. It also has to deal with the huge social and economic effects of leprosy [17,18,58]. To fight against persistent stigma, comprehensive management must include psychosocial support, economic rehabilitation programs, and community education [18,54]. Effective steroid-sparing strategies, such as MTX, contribute to holistic patient-centered care by minimizing treatment-related morbidity and allowing patients to preserve functional capacity and social engagement [18,68].

CONCLUSION

The management of steroid-dependent ENL is at a pivotal point, with new evidence indicating that methotrexate is a promising therapeutic option that overcomes significant limitations of existing

treatments [36,37]. The convergence of mechanistic rationale with preliminary clinical evidence of efficacy [36,37] and an established safety profile [43,44,45] positions MTX as a viable alternative or adjunct to conventional therapies. The ongoing MaPs trial and additional observational studies will yield conclusive evidence concerning the efficacy of MTX in diminishing glucocorticoid burden while preserving ENL control [36,37].

Switching to MTX-based management is not just a change in medication; it is a shift in the way we think about long-term disease control that is safer and more sustainable. The potential benefits include lower rates of illness and death related to glucocorticoids [15,19,22], easier access than thalidomide [26,27,51], cost-effectiveness that makes it easier to use in places with few resources [17,51,52], and better patient quality of life by reducing side effects of treatment [18,37]. However, this change must be made carefully, with the right patients chosen, systematic monitoring protocols set up, and realistic expectations about how long treatment will take and the chance of relapse [37,44].

The global health community is still working to get rid of leprosy and deal with its complications [54,55]. Methotrexate-based strategies give patients who are stuck in the cycle of chronic ENL and steroid dependence new hope. Future research elucidating optimal protocols, predictive biomarkers, and combination approaches will refine our ability to deliver personalized, effective, and safe care to this vulnerable population [35,36,42]. The way forward requires a long-term commitment to clinical research, implementation science, and patient-centered innovation. The goal is to change ENL from a long-term debilitating condition into a manageable disease that allows for full social and economic participation [54,57,58].

REFERENCES

[1] Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O, Suneetha S, Lockwood DNJ. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. Am J Trop Med Hyg. 2006;74(5):868-879.

[2] Walker SL, Balagon M, Darlong J, Doni SN, Hagge DA, Halwai V, et al. ENLIST 1: an international multi-centre cross-sectional study of the clinical features of erythema nodosum leprosum. PLoS Negl Trop Dis. 2015;9(9):e0004065.

[3] Voorend CG, Post EB. A systematic review on the epidemiological data of erythema nodosum leprosum, a type 2 leprosy reaction. PLoS Negl Trop Dis. 2013;7(10):e2440.

[4] Walker SL, Sales AM, Butlin CR, Shah M, Maghanoy A, Lambert SM, et al. A leprosy clinical severity scale for erythema nodosum leprosum: an international, multicentre validation study of the ENLIST ENL Severity Scale. PLoS Negl Trop Dis. 2017;11(7):e00057 16.

[5] Kahawita IP, Lockwood DN. Towards understanding the pathology of erythema nodosum leprosum. Trans R Soc Trop Med Hyg. 2008;102(4):329-337.

[6] Da Silva CO, Dias AA, Da Costa Nery JA, De Miranda Machado A, Ferreira H, Rodrigues TF, et al. Neutrophil extracellular traps contribute to the pathogenesis of leprosy type 2 reactions. PLoS Negl Trop Dis. 2019;13(9):e0007368.

[7] Rosa TLSA, Leal-Calvo T, Tavares IF, Mendes MA, Dias AA, Piauy MHDS, et al. Whole blood transcriptomics reveals enrichment of neutrophil activation pathways during erythema nodosum leprosum reaction. Front Immunol. 2024;15:1366125.

[8] Tavares IF, dos Santos JB, Pacheco FDS, Gandini M, Mariante RM, Rodrigues TF, et al. Mycobacterium leprae induces neutrophilic degranulation and low-density neutrophil generation during erythema nodosum leprosum. Front Med (Lausanne). 2021;8:711623.

[9] Schmitz V, Prata RBS, Barbosa MGM, Mendes MA, Brandão SS, Amadeu TP, et al. Expression of CD64 on circulating neutrophils favouring systemic inflammatory status in erythema nodosum leprosum. PLoS Negl Trop Dis. 2016;10(7):e0004955.

[10] Polycarpou A, Walker SL, Lockwood DN. A systematic review of immunological studies of erythema nodosum leprosum. Front Immunol. 2017;8:233.

[11] Sousa AL, Fava VM, Sampaio LH, Martelli CM, Costa MB, Mira MT, et al. Genetic and immunological evidence implicates interleukin 6 as a susceptibility gene for leprosy type 2 reaction. J Infect Dis. 2012;205(9):1417-1424.

[12] Barboza MFS, Hacker MD, Sales AM, Rodrigues DF, Marques DP, Noya NCS, et al. Neutrophilic leukocytosis and erythema nodosum leprosum in leprosy: insights from a retrospective observational study. Front Immunol. 2024;15:1368460.

[13] Hampton HR, Chtanova T. The lymph node neutrophil. Semin Immunol. 2016;28(2):129-136.

[14] Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol. 2018;18(2):134-147.

[15] Walker SL, Lebas E, Doni SN, Lockwood DNJ, Lambert SM. The mortality associated with erythema nodosum leprosum in Ethiopia: a retrospective hospital-based study. PLoS Negl Trop Dis. 2014;8(3):e2690.

[16] Negera E, Walker SL, Girma S, Doni SN, Tsegaye D, Lambert SM, et al. Clinico-pathological features of erythema nodosum leprosum: a case-control study at ALERT Hospital, Ethiopia. PLoS Negl Trop Dis. 2017;11(10):e0006011.

[17] Chandler DJ, Hansen KS, Mahato B, Darlong J, John A, Lockwood DN. Household costs of leprosy reactions (ENL) in rural India. PLoS Negl Trop Dis. 2015;9(1):e0003431.

[18] Bowers B, Butlin CR, Alam K, Lockwood DNJ, Walker SL. Health-related quality of life amongst people affected by erythema nodosum leprosum in Bangladesh: a cross-sectional study. Lepr Rev. 2017;88(4):488-498.

[19] Nabarro LEB, Aggarwal D, Armstrong M, Lockwood DNJ. The use of steroids and thalidomide in the management of erythema nodosum leprosum: 17 years at the Hospital for Tropical Diseases, London. Lepr Rev. 2016;87(2):221-231.

[20] Van Brakel WH, Nicholls PG, Das L, et al. The INFIR Cohort Study: investigating prediction, detection and pathogenesis of neuropathy and reactions in leprosy. Lepr Rev. 2005;76(1):14-34.

[21] Compston J. Glucocorticoid-induced osteoporosis: an update. Endocrine. 2018;61(1):7-16.

[22] Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30.

[23] Walker SL, Waters MF, Lockwood DN. The role of thalidomide in the management of erythema nodosum leprosum. Lepr Rev. 2007;78(3):197-215.

[24] Upputuri B, Pallapati MS, Tarwater P, Srikantam A. Thalidomide in the treatment of erythema nodosum leprosum (ENL) in an outpatient setting: a five-year retrospective analysis. PLoS Negl Trop Dis. 2020;14(10):e0008678.

[25] Kaur I, Dogra S, Narang T, De D. Comparative efficacy of thalidomide and prednisolone in moderate to severe erythema nodosum leprosum: a randomized study. Australas J Dermatol. 2009;50(3):181-185.

[26] Pannikar V. The return of thalidomide: new uses and renewed concerns. Lepr Rev. 2003;74(3):286-288.

[27] World Health Organization. Guidelines for the management of severe erythema nodosum leprosum (ENL) reactions. Geneva: WHO; 2021.

[28] Balagon M, Saunderson PR, Gelber RH. Does clofazimine prevent erythema nodosum leprosum? Lepr Rev. 2011;82(3):213-221.

[29] Lambert SM, Nigusse SD, Alembo DT, Walker SL, Nicholls PG, Idriss MH, et al. Ciclosporin vs prednisolone in erythema nodosum leprosum: two randomized, double-blind pilot studies. PLoS Negl Trop Dis. 2016;10(2):e0004149.

[30] Narang T, Ashraf R, Kaushik A, Dogra S. Apremilast in chronic and recurrent ENL: a prospective pilot study. J Eur Acad Dermatol Venereol. 2022;36(1):e43-e45.

[31] Brown PM, Pratt AG, Isaacs JD. Mechanism of action of methotrexate in rheumatoid arthritis. Nat Rev Rheumatol. 2016;12(12):731-742.

[32] Cronstein BN, Aune TM. Methotrexate and its mechanisms of action. Nat Rev Rheumatol. 2020;16(3):145-154.

[33] Chan ES, Cronstein BN. Methotrexate—how does it really work? Nat Rev Rheumatol. 2010;6(3):175-178.

[34] Cutolo M, Sulli A, Pizzorni C, Seriolo B, Straub RH. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Ann Rheum Dis. 2001;60(8):729-735.

[35] Stamp LK, Roberts RL. Genetic polymorphisms of the folate pathway and methotrexate therapy. Pharmacogenomics. 2011;12(10):1449-1463.

[36] de Barros B, Lambert SM, Shah M, Pai VV, Darlong J, Rozario BJ, et al. Methotrexate and prednisolone study in ENL (MaPs in ENL): protocol. BMJ Open. 2020;10(11):e037700.

[37] Jaume L, Hau E, Monsel G, Mahé A, Bertolotti A, Petit A, et al. Methotrexate as a corticosteroid-sparing agent in leprosy reactions: a French multicenter study. PLoS Negl Trop Dis. 2023;17(4):e0011238.

[38] Hossain D. Using methotrexate to treat patients with ENL unresponsive to steroids and clofazimine: report of 9 patients. Lepr Rev. 2013;84(1):105-112.

[39] Kar BR, Babu R. Methotrexate in resistant ENL. Int J Lepr Other Mycobact Dis. 2004;72(4):480-482.

[40] Rahul N, Sanjay KS, Singh S. Effectiveness of methotrexate in prednisolone- and thalidomide-resistant ENL: report of three cases. Lepr Rev. 2015;86(4):379-382.

[41] Fajardo TT Jr, Villahermosa L, Cruz EC, Tillman S, Franzblau SG, Cellona RV, et al. Methotrexate treatment for type 1 leprosy reactions. Arch Dermatol. 2007;143(7):863-867.

[42] Sales-Marques C, Cardoso CC, Alvarado-Arnez LE, et al. IL6 and NOD2 polymorphisms are risk factors for inflammatory reactions in leprosy. PLoS Negl Trop Dis. 2017;11(5):e0005754.

[43] Swierkot J, Szechiński J. Methotrexate in rheumatoid arthritis. Pharmacol Rep. 2006;58(4):473-492.

[44] Warren RB, Weatherhead SC, Smith CH, Exton LS, Mustapa MFM, Kirby B, et al. BAD guidelines for prescribing methotrexate. Br J Dermatol. 2016;175(1):23-44.

[45] Visser K, van der Heijde D. Optimal methotrexate dosage and route in RA: systematic review. Ann Rheum Dis. 2009;68 (7):1094-1099.

[46] Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate and risk of lung disease: systematic review. BMJ. 2015;350:h1269.

[47] Wagenaar I, Post E, Brandsma W, et al. Effectiveness of 32 vs 20 weeks of prednisolone in recent nerve function impairment. PLoS Negl Trop Dis. 2017;11(10):e0005952.

[48] Feuth M, Brandsma JW, Faber WR, Bhattarai B, Feuth T, Anderson AM. ENL in Nepal: retrospective study of clinical features and response to treatment. Lepr Rev. 2008;79 (3): 254-269.

[49] Girdhar A, Chakma JK, Girdhar BK. Pulsed corticosteroid therapy in chronic recurrent ENL: pilot study. Indian J Lepr. 2002;74(3): 233-236.

[50] Ramu G, Girdhar A. Treatment of steroid-dependent recurrent lepra reaction with thalidomide + clofazimine. Lepr India. 1979;51 (4):497-504.

[51] World Health Organization. WHO Model List of Essential Medicines. 22nd list. Geneva: WHO; 2021.

[52] Hoekstra M, van Ede AE, Haagsma CJ, et al. Factors associated with toxicity and efficacy of methotrexate in RA. Ann Rheum Dis. 2003;62(5):423-426.

[53] Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive early methotrexate treatment for remission (CAMERA trial). Ann Rheum Dis. 2007;66(11):1443-1449.

[54] World Health Organization. Global leprosy update, 2022: new paradigm control to elimination. Wkly Epidemiol Rec. 2023;98(35): 409-430.

[55] Franco-Paredes C, Marcos LA, Henao-Martínez AF, Rodríguez-Morales AJ. Cutaneous mycobacterial infections. Clin Microbiol Rev. 2018;32(1):e00069-18.

[56] Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin Microbiol Rev. 2006;19(2):338-381.

[57] Walker SL, Saunderson P, Kahawita IP, Lockwood DN. International workshop on ENL – ENLIST formation. Lepr Rev. 2012;83(4):396-407.

[58] Lockwood DNJ, Saunderson PR. Nerve damage in leprosy. Int Health. 2012;4(2):77-85.

[59] Wankhade VH, Debnath P, Singh RP, Sawatkar G, Bhat DM. Severe and uncommon ENL variants: retrospective study. Int J Mycobacteriol. 2019;8(1):29-34.

[60] Darlong J, Govindharaj P, Charles DE, Menzies A, Mani S. Experiences with thalidomide for ENL. Lepr Rev. 2016;87(2):211-220.

[61] Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years' experience. Int J Lepr. 2004;72(2):125-133.

[62] Lockwood DN. Leprosy. In: Burns DA, Breathnach SM, Cox NH, Griffiths CEM, editors. Rook's Textbook of Dermatology. 7th ed. Oxford: Blackwell Publishing; 2004. p.1215-1235.

[63] Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits TNF-α production by monocytes. J Exp Med. 1991;173(3):699-703.

[64] Andrade PR, Pinheiro RO, Sales AM, et al. Type 1 reaction in leprosy: tissue immunity insights. Expert Rev Clin Immunol. 2015;11(3):391-407.

[65] Costa MB, Hungria EM, Freitas AA, Sousa ALOM, Jampietro J, Soares FA, et al. Tregs and Th17 cytokines in leprosy type 1 vs type 2 reactions. PLoS One. 2018;13(6):e0196853.

[66] Bathula S, Sardana K, Khurana A. Low-dose thalidomide in steroid-dependent ENL: cost-effective option and need for trials. Lepr Rev. 2023;94(1):81-85.

[67] Savitha B, Sardana K, Kumari R, Khurana A, Sinha S, Sachdeva S. Rapid response to low-dose thalidomide in severe steroid-recalcitrant ENL. Am J Trop Med Hyg. 2022;106(1):51-53.

[68] Cruz VA, de Albuquerque CP, Guimarães MFBR, Dionello CDF, Ribeiro SLE, de Souza VA, et al. Interface between leprosy and immune-mediated rheumatic diseases. Front Med (Lausanne). 2023;10:1239775.

[69] de Barros B, Pierce R, Sprenger C, Ong ELH, Walker SL. COVID-19 vaccination and leprosy: A UK hospital-based retrospective cohort study. PLoS Negl Trop Dis. 2023;17(8): e0011493.

[70] Mowla MR, Ara S, Rahman AFMM, Tripura SP, Paul S. Leprosy reactions in the post-elimination stage: The Bangladesh experience. J Eur Acad Dermatol Venereol. 2017;31(4): 705-711.