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Kesya Kimberly
Dr. Sitanala Hospital, Tangerang, Indonesia

Siti Aisha Nabila Ferina
Dr. Sitanala Hospital, Tangerang, Indonesia

Prima Kartika Esti
Department of Dermatology & Venereology, Dr. Sitanala Hospital, Tangerang, Indonesia

Review Article

Immunomodulators in leprosy: A narrative review

Kesya Kimberly[1], Siti Aisha Nabila Ferina[1], Prima Kartika Esti[2]

1. Dr. Sitanala Hospital, Tangerang, Indonesia
2. Department of Dermatology & Venereology, Dr. Sitanala Hospital, Tangerang, Indonesia

Email: hellokesyakim@yahoo.com

Abstract

Background: Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. Current therapeutic regimen, like the multidrug therapy (MDT), are effective in treating most cases, but new cases continue to emerge in Indonesia every year. While multidrug therapy alone is adequate for treating leprosy, there is a need for adjuvant treatment options to boost the host's immune system to prevent the worsening of leprosy and reduce the activation of *M. leprae*, such as immunomodulators.
Discussion: Immunomodulators are drugs that can stimulate the body's natural and adaptive defense mechanisms, acting as either immunosuppressants or immunostimulants. To understand how immunomodulatory drugs (IMiDs) work, it is important to understand the role of immunity. This article reviews the role of immunity in leprosy and discusses various immunomodulators that have been developed or investigated to enhance the host's immune system. Substances like levamisole, thalidomide, zinc, selenium, as well as vitamins A, D, E, and C have been clinically tried in various combinations and durations, showing promise as immunomodulating agents.
Conclusion: Studies have suggested that immunomodulating agents may be considered as adjuncts to MDT to enhance the elimination and clearance of bacteria, making them potential recommendations for leprosy treatment.

Keywords*: immunomodulators, immunotherapy, leprosy, Morbus Hansen*

Background

Morbus Hansen, or leprosy, is a chronic illness caused by an infection with *Mycobacterium leprae.*[1] Although treatment with multidrug therapy (MDT) has been proven to be effective, new cases of leprosy continue to emerge every year. According to the World Health Organization (WHO), in 2019 there were 202,256 new cases of leprosy reported worldwide, spanning 161 countries across six WHO regions.[2] The Indonesian Ministry of Health's data and information center reported 17,202 new leprosy cases in 2018, making Indonesia the third-highest ranked country in terms of leprosy cases, following India and Brazil.[3]

Multidrug therapy is needed to prevent nerve damage and control the growth of bacteria; however, at times, the treatment is inadequate. To achieve successful treatment for infectious diseases, it is important to understand more about the human immune response in fighting pathogens. Immune-based treatments are beneficial for both malignant and infectious diseases.[4] A 2020 systematic review of *in vitro* and *in vivo* studies concluded that there is a parallel connection between pathogenic diseases and the host's immune response. Therefore, treatment options that can enhance the host's immune system are needed to improve tolerance to leprosy.[5] Additionally, these treatments are also expected to reduce the risk of *Mycobacterium leprae* reactivation. To achieve these goals, effective prophylactic and therapeutic treatment options are necessary. Immunomodulators, which include drugs, vitamins, and vaccines, have been studied and found to be effective in killing and eliminating bacteria in the bodies of leprosy patients.[6,7] Vaccines, unlike drugs, are used for prophylaxis and are administered early in life to stimulate the immune system and produce

antibodies to fight *M. leprae*.[8] In this review, we will focus on various types of immunomodulator drugs and their roles in leprosy.

Discussion

Role of immunity in leprosy

M. leprae is a cellular obligate bacterium; therefore, the body's immunity plays an important role in the course of leprosy. A 2011 systematic review stated that the clinical manifestations of *M. leprae* infection vary depending on the condition of the host' cellular immunity.[9] *M. leprae* enters through the respiratory tract, passes through the body's immune system, where macrophages and neutrophils try to destroy the bacteria in the early phase. However, if the immune system is weak, the bacteria cannot be destroyed by the body's immune system, and subsequently enter the bloodstream along with monocytes, and grow within the body's cells (Trojan Horse phenomenon).[9] The body's immune response to *M. leprae* can be divided into two categories: Innate immune response and adaptive/acquired immune response. The adaptive immune response works more slowly than the innate immune response. The innate immune response is the body's first line of defense against external and internal attacks. This immune response is activated immediately when infection occurs to eliminate *M. leprae*.[10,11] The innate immune response to *M. leprae* is activated by pattern recognition receptors (PRR), which are a combination of toll-like receptors (TLR) and nucleotides-binding oligomerization domain (NOD)-like receptors (NLR). Pattern recognition receptors can recognize endogenous molecules in cells damaged by *M. leprae*, known as damage-associated molecular patterns (DAMPs).

The formation of DAMPs can cause chronic inflammation.[11] Toll-like receptors are receptors that protect the body from infection. *M. leprae* has the potential to bind to TLRs, particularly TLR-2. *M. leprae* damages Schwann cells and causes neuritis in patients because it can activate TLR-1 and TLR-2 in Schwann cells.[12-14] The activation of TLR-1 and TLR-2 caused by *M. leprae* is related to types 1 and 2 leprosy reactions (Figure 1).[14] At the same time, NLRs function as receptors that can identify pathogens in the cytoplasm. Humans have 23 different types of NLRs, including nucleotide-binding oligomerization domain (NOD) and leucine-rich repeats (LRRs).

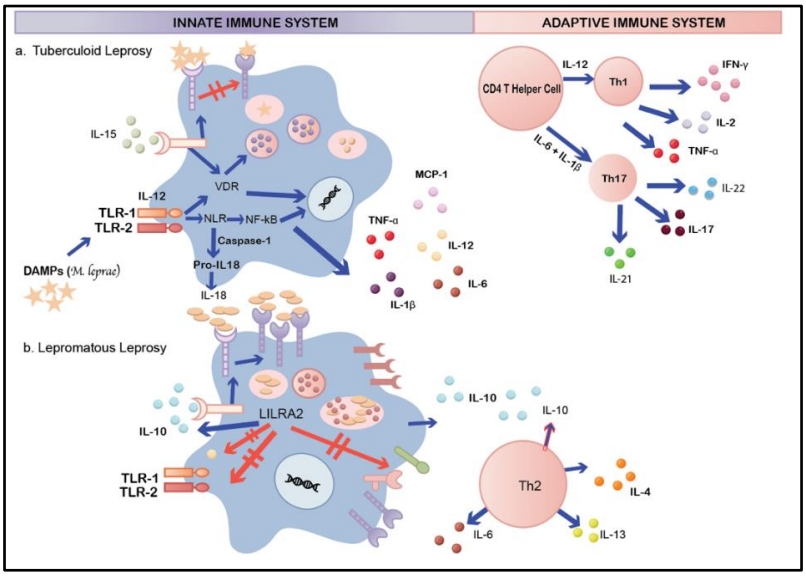

Figure 1. Immune Response in Types of Leprosy.
A. In patients with tuberculoid leprosy (TT), the innate immune response is activated by DAMPs through toll-like receptors (TLR1 and TLR2). Interleukin (IL)-15 stimulates; VDR program in macrophages. These events stimulate CD4 T helper cells and promote Th1 T cell response and Th17 response. B. In patients with lepromatous leprosy (LL), immune complexes trigger the production of IL-10 and increase phagocytosis of DAMPs, then induce Th2 immune profile with the production of anti-inflammatory cytokines IL-4, IL-10, IL-13, and IL-6.
CD4: clusters of differentiation 4; DAMPs: damage-associated molecular patterns; IL: interleukin; LILRA2: leukocyte immunoglobulin-like receptor subfamily A member 2; TLR: toll-like receptors; Th: T helper; TNF: tumor necrosis factor; VDR: vitamin D receptor

M. leprae is an intracellular bacterium with the ability to enter the cytoplasm and interact with the NLRs. The NLRs will then activate caspase-1 through Apoptosis Associated Speck-like protein (ASC), which plays a role in activating pro-IL-1β and pro-IL-18 proinflammatory cytokines into active IL-1β and IL-18, which can induce cell death or apoptosis (Figure 2).[15,16] Nucleotide-binding oligomerization domain-2 (NOD-2), a component of NLRs, plays a crucial role in the course of leprosy. It can be activated through nuclear factor Kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and interferon regulatory factor (IRF). NOD-2 is believed to be associated with type 1 and 2 leprosy reactions and can exacerbate the course of leprosy.[11-13]

In tuberculoid leprosy, the innate immune response will be activated through the activation of toll-like receptors (TLR1 and TLR2) by DAMPs, the expression of which will promote the activation of IL-18 and NF-κB. Cytokines such as IL-12 and IL-15 are produced initially on the innate immune response to regulate macrophage function. IL-15 then induced the activation of vitamin D receptor (VDR), which plays a crucial role in gene expression. These events will promote the activation of Th1 response (interferon [IFN]-γ, IL-2, tumor necrosis factor [TNF]-α) and Th17 response (IL-22, IL-17, and IL-21). In patients with lepromatous leprosy, the expression of leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2) plays a significant role. The expression of LILRA2 inhibits TLR1 and TLR2 expression but triggers the macrophages to produce IL-10 and inhibit IL-12, which impairs the macrophage's phagocytic ability. This event leads to the accumulation of DAMPs inside the cell, which results in the accumulation of lipid droplets or "foamy macrophages" and decreased apoptosis ability due to lack of IL-1β and IL-18 (Figure 1).[15]

A 2016 cross-sectional study in 19 leprosy patients reported that the expression of caspase-1 was found in cell lesions of all types of leprosy. Correspondingly, the expression of the IL-18 gene was observed in tuberculoid-type leprosy skin lesions and showed a decrease in lepromatous type of leprosy. This variation may be attributed to the body's immunity against *M. leprae*, as the amount of IL-18 expression is contingent upon this. Consequently, the study concluded that a significant positive correlation exists between the expression of caspase-1 and IL-18 in the skin lesions of leprosy patients. Furthermore, IL-18 interacts with IL-12 and IL-2 to form IFN-γ and TNF-α, both of which play crucial roles in the course of leprosy (Figure 1).[17]

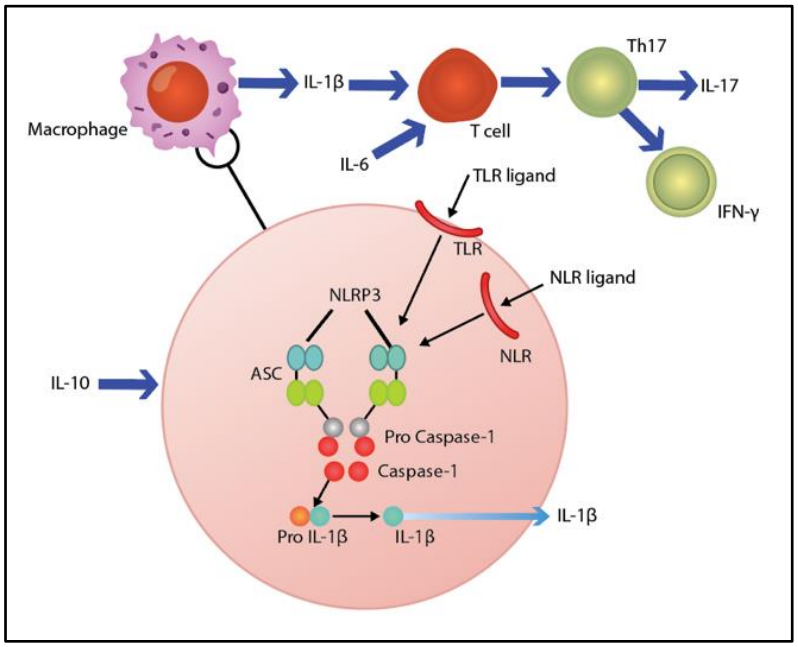

Figure 2. Caspase Pathway.
TLR and NLR activation in macrophages will promote NLR (NLRP3) expression. This, in turn, activates pro caspase-1 into caspase-1 through ASC protein that turns pro IL-1β into its active form (IL-1β).
ASC: apoptosis-associated speck-like protein; IFN: interferon; IL: interleukin; NLRP3: nucleotides-binding oligomerization domain (NOD)-like receptors pyrin domain containing 3; NLR: nucleotides-binding oligomerization domain (NOD)-like receptors; TLR: toll-like receptor; Th: T helper

The role of immunomodulator in leprosy

Immunomodulators are drugs that can stimulate the body's natural and adaptive defense mechanisms, allowing the immune response to function properly. They can act as immunosuppressants or immunostimulants. Our discussion focuses on immunomodulatory drugs that help enhance the body's ability to fight infection and leprosy.[8] Leprosy presents as a spectrum of tuberculoid and lepromatous forms. In tuberculoid leprosy (TT), a polarization of Th1 occurs, which results from the activation of cytotoxic T cells (CD8+), macrophages, and bactericidal mechanisms that control the growth of *M. leprae* through IFN-γ. On the other hand, lepromatous leprosy (LL) occurs due to impaired specific cellular immunity.[4]

Immune checkpoint molecules (ICPs) play a crucial role in T-cell activation and determine the function of T-cells in decreasing the proliferation and secretion of inflammatory cytokines, such as IL-2, IFN-γ, and TNF-α. These molecules also influence the maturation of dendritic cells and the function of macrophages. ICP molecules, particularly PD-1/PD-L1 and CTLA-4, have been extensively investigated as therapeutic molecular targets in adjunct antimicrobial therapy for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and tuberculosis (Figure 1).[4]

The immune checkpoint (ICP) mechanism starts from the first signal, which occurs when the antigen attaches to major histocompatibility complex (MHC) II carried by antigen-presenting cells (APCs) and interacts with the T-cell receptor (TCR) of naïve T-cells. A second signal occurs when B7 binds to the CD28 receptor on these cells. When both signals are active, T-cells, such as T-helper (Th) cells and cytotoxic T-cell lymphocytes, release cytokines (IL-6, IL-2, IFN-γ, IL-12, and TNF-α) and cytotoxic compounds. However, the presence of chronic immune stimulation, resulting from continuous exposure to antigens, disrupts cellular-specific immunity. The expression of other molecules, such as PD-1, TIGIT, lymphocyte-activation gene 3 (LAG-3), and T lymphocyte-associated cytotoxic protein 4 (CTLA-4), on lymphocytes and their respective partners on the APC surface (PD-L1, CD122/155, MHC class II, and B7), induces specific T-cells, which cause the disease to spread more rapidly. ICP inhibitors, such as PD-1, CTLA-4, LAG-3, and TIGIT, can be a strategy for controlling leprosy, especially in LL patients.[4] Immunomodulatory drugs contain components that can block the ICP molecule. These drugs can modulate the immune system in patients with latent or active leprosy infection, helping to control the replication of *M. leprae* better.[4,18]

Types of immunomodulators and their use in leprosy

a. Levamisole

There are different types of immunomodulators used in leprosy treatment, with one example being levamisole. Derived from imidazothiazole, levamisole is an anti-helminthic drug. Levamisole has been shown to have an activity as an immunomodulator for several skin diseases, including leprosy. Levamisole works as a nicotinic acetylcholine receptor agonist, targeting the activity of macrophages and T-cells. It strengthens phagocytic activity and chemotaxis; and slows down skin hypersensitivity process.[18] Levamisole plays a role in decreasing the activation and proliferation of human T helper cells (CD4+) and CD8+ *in vitro*.

Levamisole also shows a significant reduction in IL-10. In addition to its inhibitory proliferation effects, levamisole upregulates the secretion of T-cell-associated pro-inflammatory cytokines such as IL-2, IL-4, IL-13, IFN-γ, and TNF-α.[19] Two *in vitro* and *in vivo* testing concluded that levamisole directly suppresses T-cell proliferation and stimulates the production of Th1 by rapidly increasing the secretion of IFN-γ and Th2 pathways (IL-4, IL-10, IL-12, IL-13, TNF-α, and IL-1β) (Table 1).[19,20]

In leprosy, levamisole can be used as a therapeutic option to reduce the activity of *M. leprae.* Levamisole can be used as an adjuvant drug alongside MDT.[18] A 2016 comparative randomized clinical trial in India concluded that levamisole can shorten the length of leprosy treatment when combined with MDT. It can also control the spread of the disease. This study compared the administration of MDT monotherapy, MDT plus 150 mg levamisole twice a week, and MDT plus 400 mg albendazole once a week for one month, for a total of three months. The analysis revealed that MDT combined with levamisole showed a significant reduction in Bacterial Index (BI) compared to other groups.[21,22]

According to a case-non-case study in 2021, levamisole has several adverse reactions as an immunomodulator, such as convulsions, thrombocytopenia, neuropathy, severe skin disorders (Stevens-Johnson syndrome or toxic

epidermal necrolysis and acute generalized exanthematous pustulosis), vertigo, arthralgia/myalgia, neutropenia, and tachycardia. More serious adverse reactions, such as nervous system disorders, gastrointestinal disorders, musculoskeletal tissue disorders, and vascular disorders, were also reported in some patients.[23]

b. Thalidomide

Thalidomide is a drug derived from synthetic glutamic acid and can act as an anti-inflammatory, immunomodulatory, and anti-angiogenic agent due to its inhibition of vascular endothelial growth factor (VEGF). Thalidomide is an immunomodulatory drug that can be used for dermatological diseases, such as psoriasis, prurigo nodularis, senile pruritus, dermatitis, pyoderma gangrenosum, and type 2 leprosy reaction or erythema nodosum leprosum (ENL).[7]

A case study of patient with leprosy reaction in 2016 reported that thalidomide is effective in providing a 90% cure for patients with ENL. Thalidomide has an inhibitory effect on TNF-α, which is produced by monocytes. High levels of serum TNF-α have been observed in ENL patients. Therefore, with the administration of thalidomide, patients' serum levels of TNF-α could be significantly reduced, resulting in clinical improvement.[24] Recent *in vitro* immunology studies on 24 rats (2021) and human cancer cells (2023) support that as an immunomodulatory agent, thalidomide and its analogs significantly suppress pro-inflammatory IL-1β, IL-6, TNF-α, VEGF, and NF-κB gene expressions ($p < 0.05$), as shown in Table 1.[25,26]

A 5-year retrospective cohort study on leprosy patients in India reported that thalidomide is effective in the treatment of ENL. Thalidomide has been proven to be useful as a steroid-sparing agent for controlling leprosy reactions due to its anti-inflammatory and immunomodulatory properties. This study, conducted on 102 patients with ENL who were given thalidomide, reported that 68 patients (66.7%) showed improvement with a significant decrease in BI. However, the use of thalidomide should be closely monitored with dose limitations, especially in pregnant women, due to its teratogenic and neurotoxic effects.[27,28]

A 2016 randomized comparative study compared 4 treatment regimens of ENL; prednisolone monotherapy and thalidomide monotherapy for the treatment of the first episode of ENL, and prednisolone plus thalidomide and prednisolone plus clofazimine for the treatment of recurrent ENL. The study concluded that thalidomide monotherapy had an efficacy of 93.75% for the first episode of ENL, compared to the 58.8% of prednisolone monotherapy ($p < 0.05$). As for recurrent patients, the efficacy of prednisolone plus thalidomide was 82.35%, compared to the 62.5% of prednisolone plus clofazimine ($p < 0.05$). This shows that thalidomide provides better outcomes for the treatment of ENL.[29] Similar and recent clinical trial from, which compared the efficacy of prednisolone plus thalidomide (group A) and prednisolone plus clofazimine (group B) on 30 patients with ENL, concluded that group A had better reduction of reaction severity score (RSS), visual analog scale (VAS), and recurrence of ENL compared to group B ($p < 0.05$).[30]

The dosage and duration of thalidomide administration in leprosy have been fields of uncertainty. The recommended dosage of thalidomide proven to control ENL is 300 mg daily for the first month, followed by 200 mg daily in the second month, and 100 mg daily in the third month, followed by 50 mg daily until complete recovery.[27] A prospective non-randomized clinical trial conducted on 42 patients with ENL concluded that 100 mg of thalidomide daily for 6 months was effective as preventive therapy of ENL with no side effects.[31]

A case study from Surabaya, Indonesia reported the usage of 50 mg thalidomide twice daily (day 1-22) as a sparing agent of methylprednisolone (MP) and immunomodulator. The dose was subsequently changed to 100 mg daily on day 23. After 1 month, 50 mg thalidomide daily was continued as MP was discontinued. This approach successfully controls ENL in this patient with no serious adverse event except for pain in the legs and cramps in the hands during treatment.[24] Six serial case studies on immunosuppressed patients reported a variety of side effects of thalidomide as an immunomodulator, including central neurotoxicity (short-term memory, dementia-like amnesia, expressive aphasia, dysarthria, lethargy, and coma). All symptoms were reversible and resolved after discontinuation of thalidomide.[32] Other side effects reported include nausea, vomiting, drowsiness, constipation, pedal edema, and dry mouth.[27] Overall, thalidomide has shown promise as an effective treatment for ENL. However, careful monitoring and adherence to dosage guidelines are necessary to minimize potential side effects, especially in pregnant women.

c. Zinc (Zn)

Zinc is a micronutrient that is very important for maintaining the balance of the body's innate

immune system. Zinc deficiency can inhibit the body's immune response to eliminate bacteria that enter the body and increase the production of NF-κB, which causes the body to become more resistant to infection.[33] Zinc deficiency can also reduce the activity of Th1 responses and other cytokines. In leprosy patients, zinc deficiency can reduce the response of inflammatory cytokines, such as IFN-γ and IL-2, which play an important role in controlling *M. leprae* infection. Zinc can stimulate the production of IL-2 and control bacterial activity and growth within the body (Table 1).[34,35]

A clinical controlled trial on 63 patients with leprosy showed a significant correlation between BI and total zinc level. This study concluded that there was a gradual reduction in serum zinc level as the BI level got higher, which resulted in a more severe form of leprosy ($p<0.001$).[36] Another cross-sectional study on 100 patients with leprosy found that serum level of zinc was significantly lower in PB leprosy compared to the healthy controls ($p<0.001$), while there was no significant difference between PB and MB.[37]

Administration of zinc as an adjunct to MDT has been shown to significantly improve the patient's clinical condition. Zinc given as an adjuvant to dapsone in LL patients induces rapid conversion of lepromin compared to a control group without zinc administration.[36,38-40] Daily oral zinc with a dose of 200-400 mg for 3-8 months as a therapeutic agent has successfully improved the incidence of leprosy reaction compared to the control group.[36]

d. Vitamins A, D, and E

Vitamin A is an important component that plays a vital role in the immune system as it regulates several aspects of the immune response. Leprosy patients are reported to have low levels of vitamin A. Vitamin A deficiency has been associated with reduced phagocytic activity in macrophages and decreased natural killer (NK) cell activity.[41] A cross-sectional study on 34 leprosy patients that compared vitamin A levels between paucibacillary (PB) and multibacillary (MB) types of leprosy showed lower levels of vitamin A in MB type, especially in LL patients ($p=0.001$).[42] Vitamin A intake promotes the production of IL-10 and induces an anti-inflammatory response, inhibiting the production of IL-12 and TNF-α, which are implicated in the progression of leprosy. Vitamin A can be obtained from food sources, such as chicken liver, eggs, milk, red or orange fruits, and vegetables, as well as through oral supplementation (Table 1).[34,40-42] Like vitamin A, vitamin D can modulate the immune system to combat various pathogens, including *M. leprae*. Vitamin D enhances phagocytic activity and stimulates the production of antimicrobial peptides in infected macrophages and neutrophils. These peptides possess immunomodulatory properties for the innate immune system and act as immunomodulators through Vitamin D Receptor (VDR) inside macrophages. Vitamin D has been shown to activate macrophages by binding to Toll-like receptors (TLR), thereby aiding in the elimination of *Mycobacterium*, resulting in inhibition of Th1 activity (reduction of IL-12, IFN-γ, IL-6, IL-8, TNF-α, and IL-9).

In contrast, vitamin D upregulates the activation of Th2 (IL-4, IL-5, and IL-10), as described in Table 1. Although studies on vitamin D deficiency in leprosy remain limited, one recent cross-sectional study involving 20 leprosy patients concluded that there is a significant depletion in serum vitamin D levels in patients with leprosy ($p<0.001$).[43] The main sources of vitamin D are diet, UVB exposure, and supplements. Vitamin D is available in two forms, namely ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D3 is mainly provided by sunlight. It is recommended to get direct sunlight exposure for 10-15 minutes twice a week without sunscreen to get an optimal level of vitamin D3. Meanwhile, dietary sources and multivitamins mainly contain vitamin D2. Food sources rich in Vitamin D include sea fish, fish oil, egg yolks, butter, cheese, meat, or oral supplementation.[34,40,43]

Vitamin E or alpha tocopherol has a protective effect against oxidative stress in leprosy. Tocopherol, the active compound in vitamin E, exhibits an affinity for phospholipids in mitochondria, endoplasmic reticulum, and plasma membrane, safeguarding the fatty acids contained in this phospholipid membrane from oxidation. *M. leprae* has been found to damage fatty acids within the membrane. Adequate consumption of vitamin E allows tocopherol to neutralize this reaction, inhibiting the escalation of free radical formation during *M. leprae* infection. A cross-sectional study from East Sumatera on 24 leprosy subjects concluded that there was no significant correlation between vitamin E levels in PB and MB leprosy; however, MB leprosy has lower vitamin E levels than PB leprosy.[43] In a study where leprosy patients were treated with dapsone, rifampicin, and clofazimine in combination with an additional 400 IU of vitamin E for 12 months, a significant reduction in oxidative stress from lipid peroxidation (LPO) was observed, as described in Table 1.[43] Vitamin E can easily be obtained from vegetable oil, olive oil, nuts, and avocados.[34,43,44]

e. Vitamin C

The body's immune system needs an adequate and diverse diet consisting of protein, vitamins, and minerals to effectively combat infections. Vitamin C, as a powerful antioxidant, has a significant role in enhancing human immune system.[44,45] Vitamin C has the potential ability to reduce oxidative stress and affect the phagocytic ability of macrophages, interferon production, inhibit replication of DAMPs, as well as enhance the maturation of T-lymphocytes.[45]

A recent cross-sectional study on 100 patients with a new course of leprosy showed that leprosy patients have a lower level of vitamin C compared to healthy individuals (p=0.078).[39] This finding might be related to increased oxidative stress due to leprosy infection. A case-control study on 52 leprosy subjects and 100 controls in leprosy endemic area of Bangladesh also proved that most leprosy patients suffer from undernutrition, as it may be a contributing factor to low levels of serum vitamin C.[44]

f. **Selenium**

As an immunomodulator, selenium has an anti-proliferative and immune-enhancing property by way of boosting the body's innate and adaptive immune defense. Selenium has been proven to increase the activation of NK cells, CD4+ T cells, and the expression of IFN-γ.[46]

A 2018 cross-sectional study on 30 leprosy patients showed that serum selenium in patients with leprosy, especially MB type, was significantly lower than in PB leprosy patients (p=0.005), and patients with high BI correlated with low selenium levels.[47] On the other hand, a 2021 case control study in Egypt on 100 leprotic patients (50 MB and 50 PB) and 100 controls suggested that selenium level has no impact on patients with leprosy and healthy controls.[37] Although still under debate, a strong 2021 experimental study on 60 immunosuppressed mice showed that 80 mg/kg selenium supplementation as an immunomodulator can reduce the secretion of nitric oxide, IL-2, and IFN-γ.[48] The recommended dietary intake of selenium as an immunomodulator in humans as recommended by a randomized controlled trial in children and adolescents ranges from 15 µg/day for children aged 1–3 years to 70 µg/day for adolescents.[49]

Table 1. Summary of Immunomodulator Drugs in Leprosy

Immunomodulator Drugs	Effects	References
Levamisole	• Decreases CD4+ and CD8+ proliferation • Reduces IL-10 • Upregulates IL-2, IL-4, IL-13, IFN-γ, TNF-α, IL-1β	19, 20
Thalidomide	• Inhibits TNF-α and VEGF • Reduces IL-1β, IL-6	7, 24, 25, 26
Zinc	• Increases production of NF-κB • Upregulates Th1 activity, which increases IFN-γ and IL-2	33, 34, 35
Vitamin A	• Increases production of NF-κB, IFN-γ, IL-10 • Inhibits production of IL-12 and TNF-α	33, 40, 41
Vitamin D	• Activates macrophages by binding to TLR • Reduces Th1 activation • Upregulates Th2 activity	33, 40 42
Vitamin C	• Reduces oxidative stress • Enhances macrophage's phagocytic ability and interferon production, inhibits replication of DAMPs, enhances maturation of T-lymphocytes	45
Vitamin E	• Reduces oxidative stress resulting from macrophages' phagocytic activity	43
Selenium	• Increases activation of NK cells, CD4+ T cells • Increases expression of IFN	46

CD: cluster of differentiation; DAMPs: damage-associated molecular patterns; IFN: interferon; IL: interleukin; NF-κB: nuclear factor kappa B; NK: natural killer; TNF: tumor necrosis factor; TLR: toll-like receptor; VEGF: vascular endothelial growth factor

Conclusion

There are various choices of immunomodulators, in the form of drugs and vitamins, that can be used as an adjunct to MDT in leprosy. Some have been studied and shown to have a positive impact on the treatment and course of leprosy. However, proper dosage monitoring is necessary during administration to minimize the occurrence of various side effects associated with immunomodulatory drugs.

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None.

Author Contributions

KK is the main investigator and writer of this study. SANB participated in data acquisition and writing of the manuscript. PKE supervised and approved the manuscript. All authors reviewed the manuscript.

Conflict of Interest

No conflict of interest.

References

1. Chen KH, Lin CY, Su SB, Chen KT. Leprosy: A review of epidemiology, clinical diagnosis, and management. J Trop Med. 2022;2022:1.
2. World Health Organization. Towards zero leprosy: Global leprosy (Hansen's disease) strategy 2021 – 2030. New Delhi: World Health Organization, Regional Office for South-East Asia; 2017. p.9.
3. Pusat Data dan Informasi Kemenkes Republik Indonesia. Hapuskan stigma dan diskriminasi terhadap kusta. Kemenkes RI; 2018. p.3. Indonesian.
4. Lima HR, Gasparoto TH, de Souza Malaspina TS, et al. Immune checkpoints in leprosy: Immunotherapy as a feasible approach to control disease progression. Front Immunol. 2017;8:1724.
5. De Macedo CS, Lara FA, Olmo R, Schmitz V. New insights into the pathogenesis of leprosy: Contribution of subversion of host cell metabolism to bacterial persistence, disease progression, and transmission. F1000 Research. 2020;9:70.
6. Chauhan D, Kamal R, Saxena A. Therapy of leprosy-Present strategies and recent trends with immunotherapy. J Dermatol Res Ther. 2020;6(2):1-10.
7. Tarina M, Agustin T, Dachlan AS, Effendi EH. Penggunaan imunostimulan dalam bidang dermatovenereologi. Media Dermato-Venereologica Indonesiana. 2019;46(2):111-5. Indonesian.
8. Wang H. Leprosy vaccines: Development for prevention and treatment. In: Christodoulides, M. editor. Vaccines for neglected pathogens, achievements and challenges. Switzerland: Springer Cham; 2023. p.47-69.
9. Makino M. Host defense against *M. leprae*. In: Makino M, Matsuoka M, Goto M, Hatano K, editors. Leprosy science working toward dignity. Kanagawa: Tokai University Press; 2011. p.89-96.
10. White C, Franco-Paredes C. Leprosy in the 21st century. Clin Microbiol Rev. 2015;28(1):80-94.
11. Paul S, Hmar EB, Sharma HK. Strengthening immunity with immunostimulants: A review. Current Trends in Pharmaceutical Research. 2020;7(10):2582-4783.
12. Pinheiro RO, Schmitz V, Silva B, et al. Innate immune responses in leprosy. Front Immunol. 2018;9:518.
13. Jin SH, Ahn KJ, An S. Importance of the immune response to Mycobacterium leprae in the skin. Biomedical Dermatology. 2018;2:1.
14. de Sousa JR, Sotto MN, Quaresma. Leprosy as a complex infection: Breakdown of the Th1 and Th2 immune paradigm in the immunopathogenesis of the disease. Front Immunol. 2017;8:1635.
15. de Lima Fonseca AB, de Vale Simon M, Cazzaniga RA. The influence of innate and adaptive immune responses on the differential clinical outcomes of leprosy. Infect Dis Poverty. 2017;6:5.
16. Jorge KTOS, Soriani FM. Genetic variation in pattern-recognition receptors and association with leprosy. In: Ribòn W. Editor. Hansen's disease – the forgotten and neglected disease. IntechOpen; 2018. p.145-8.
17. Suwarsa O, Gunawan H, Achdiat PA. Imunitas bawaan pada kusta: Hubungan ekspresi kaspase-1 dan interleukin-18 pada lesi kulit pasien kusta. MKD. 2016;48(3):181-6. Indonesian.
18. Chauhan D, Kamal R, Saxena A. Therapy of leprosy-present strategies and recent trends with immunotherapy. J Dermatol Red Ther. 2020;6:093.
19. Khan GH, Veltkamp F, Scheper M, et al. Levamisole suppresses activation and proliferation of human T cells by the induction of a p53-dependent DNA damage response. Eur J Immunol. 2023;53(11):2350562.

20. Fu Y, Wang T, Xiu L, et al. Levamisole promotes murine bone marrow derived dendritic cell activation and drives Th1 immune response in vitro and in vivo. Int Immunopharmacol. 2016;31:57-65.
21. Mukherji T, Mukherji MB, Roy S. Comparative study on impact of the immunomodulators drugs levamisole and albendazole on multibacillary leprosy in two different medical colleges in different states and regions. Indian Journal of Research. 2016;5(10): 84-6.
22. Gupta M. Levamisole: A multi-faceted drug in dermatology. Indian J Dermatol Venereol Leprol. 2016;82(2):230-6.
23. Campillo JT, Eiden C, Boussinesq M, et al. Adverse reactions with levamisole vary according to its indications and misuse: A systematic pharmacovilance study. Br J Clin Pharmacol. 2022;88(3):1094-106.
24. Habibie DP, Listiawan MY. The use of thalidomide in steroid dependent continuous erythema nodosum leprosum leprosy patient: A case report. Berkala Ilmu Kesehatan Kulit dan Kelamin. 2016;28(2):168-74.
25. Santana AC, Andraus W, Silva FMO, et al. Immunomodulatory effects of thalidomide in an experimental brain death liver donor model. Scientific Reports. 2021;11:19221.
26. Kotb AR, Abdallah AE, Elkady H, et al. Design, synthesis, anticancer evaluation, and *in silico* ADMET analysis of novel thalidomide analogs as promising immunomodulatory agents. RSC Adv. 2023;13(16):10488-502.
27. 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 from a leprosy referral centre in India. PLoS Negl Trop Dis. 2020;14(10):e0008678.
28. Anant JK, Inchulkar SR, Bhagat S. Medical termination of pregnancy-a review. World Journal of Pharmaceutical and Life Sciences. 2018;4(10):65-9.
29. Kar HK, Gupta L. Comparative efficacy of four treatment regimens in type 2 leprosy reactions (prednisolone alone, thalidomide alone, prednisolone plus thalidomide and prednisolone plus clofazimine). Indian J Lepr. 2016;88(1):29-38.
30. PK Mishra SR, Samal R, Behera B. Thalidomide and steroid in the management of erythema nodosum leprosum. Indian J Pharmacol. 2022;54(3):177-82.
31. de Ayres Putinatti MS, Lastoria JC, Padovani CR. Prevention of repeated episodes of type 2 reaction of leprosy with the use of thalidomide 100 mg/day. An Bras Dermatol. 2014;89(2): 266-73.
32. Patel UH, Mir MA, Sivik JK, Raheja D, Pandey MK, Talamo G. Central neurotoxicity of immunomodulatory drugs in multiple myeloma. Hematol Rep. 2015;7(1):5704.
33. Hojyo S, Fukada T. Roles of zinc signaling in the immune system. Journal of Immunology Research. 2016;2016:21.
34. Vazquez CMP, Netto RSM, Barbosa KBF, de Moura TR, de Almeida RP. Micronutrients influencing the immune response in leprosy. Nutr Hosp. 2014;29(1):26-36.
35. Dwivedi VP, Banerjee A, Das I, et al. Diet and nutrition: An important risk factor in leprosy. Microb Pathog. 2019;137:103714.
36. Jain P, Khare V, Koshti A, Malik R, Bhimte B. Serum zinc level estimation-comparison between normal control and in leprosy patients: clinical presentations. New Frontiers in Medicine and Medical Research. 2021;1:1-5.
37. Khalid HN, Mostafa MI, Attia NS, Bazid HASE. Serum level of selenium, zinc, and vitamin c and their relation to the clinical spectrum of leprosy. J Infect Dev Ctries. 2022;16(3):491-9.
38. Gupta M, Mahajan VK, Mehta KS, Chauhan PS. Zinc therapy in dermatology: A review. Dermatol Res Pract. 2014;2014:709152.
39. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. Nutrients; 2017;9(12):1286.
40. Klowak M, Boggild AK. A review of nutrition in neuropathic pain of leprosy. Ther Adv Infectious Dis. 2022;9:1-19.
41. Dalimunthe DA, Hazlianda CP, Partogi D. Analysis of vitamin a in leprosy patients. Bali Medical Journal (Bali MedJ). 2021;10(2):746-8.
42. Darus NIM, Lubis RD, Jusuf NK. Analysis of serum vitamin d level in leprosy patients. Bali Medical Journal (Bali MedJ). 2019;8(3):795-9.
43. Hazlianda CP, Dalimunthe DA, Partogi D. Analysis of vitamin e in leprosy patients. Journal of Pakistan Association of Dermatologists. 2023;33(4):1238-41.
44. Wagenaar I, van Muiden L, Alam K, et al. Diet-related rick factors for leprosy: a case control study. PLoS Negl Trop Dis. 2015;9(5):e0003766.
45. Hemila H. Vitamin C and infections. Nutrients. 2017;9(4):339.
46. Chen G, Yang F, Fan S, et al. Immunomodulatory roles of selenium nanoparticles: Novel arts for porential immunotherapy stratery development. Front Immunol. 2022;13:956181.
47. Partogi D, Dalimunthe DA, Hazlianda CP. A study of selenium in leprosy. Open Access Maced J Med Sci. 2018;6(3):485-7.

48. Zhang J, Gao S, Li H, Cao M, Li W, Liu X. Immunomodulatory effects of selenium-enriched peptides from soybean in cyclophosphamide-induced immunosuppressed mice. Food Sci Nutr. 2021;9(11):6322-4.
49. Agostoni C, Canani RB, Fairweather-Trait S. Scientific opinion on dietary reference values for selenium. EFSA J. 2014;12(10):3846.