The 1st International Innovation Technology Proceedings
Vol 1 No 1 (2023): October
E-ISSN: 3030-9948
https://iite-proceeding.poltekindonusa.ac.id

A CYTOKINE RESPONSE IN LEPROSY: Literature Review

Emma Ismawatie[1*], Inas Hasna Azizah[2], Yulita Maulani[3]
[1]Medical Laboratory Technology Study Program, Polytechnic of Indonusa, Surakarta, Indonesia
[2]Master Course in Immunology, Postgraduate School, Universitas Airlangga, Indonesia
*Corresponding author email: emmaismawatie@poltekindonusa.ac.id

Received:	Revised:	Accepted:	Published:
July 8, 2023	July 15, 2023	July 27, 2023	October 5, 2023

Abstract

Leprosy is an infection that has strategic effects on society, especially in the economic sector. This diseases is caused by Mycobacterium leprae. Therapy based on the immune response caused by M. leprae infection, especially the cytokines response is an effective choice considering that each patients has a different immune response in dealing with M. leprae infection. This article aimed to identify cytokines that play a role in M. leprae. The innate and adaptive immune response has an important role against this infection.

Key words: *cytokines, immune response, Leprosy*

1. Introduction

Leprosy is a chronic disease caused by *Mycobacterium leprae* [1][2]. This infection attacks the skin and peripheral nerves [3]. The bacterium *M. leprae* is the only mycobacterial infection that causes widespread demyelinating neuropathy, which results in leprosy morbidity, autoamputation of the digits and blindness. The debilitating morbidity is associated with axonal demyelination resulting from the direct interaction of *M. leprae*-specific PGL-1 with GLIA myelination and subsequent infection [2]. Therapy has been proven effective in curing leprosy [4]. According to WHO data in 2020 around 127,558 new cases were found. Southeast Asia ranks first in the most cases of Leprosy. Indonesia is still the 3rd largest country in the world with the most Leprosy cases. A total of 9,061 new cases were found in 2020 [5].

The *M. leprae* bacteria are intracellular organisms that cannot move into the cytoplasm [6]. However, in a study by Van *et al* (2007) reported that *M. leprae* can translocate into the cytoplasm so that it can interact with the nucleotide-binding oligomerization domain (NOD)-like receptors (NLR) [7].

The 1st International Innovation Technology Proceedings
Vol 1 No 1 (2023): October
E-ISSN: 3030-9948
https://iite-proceeding.poltekindonusa.ac.id

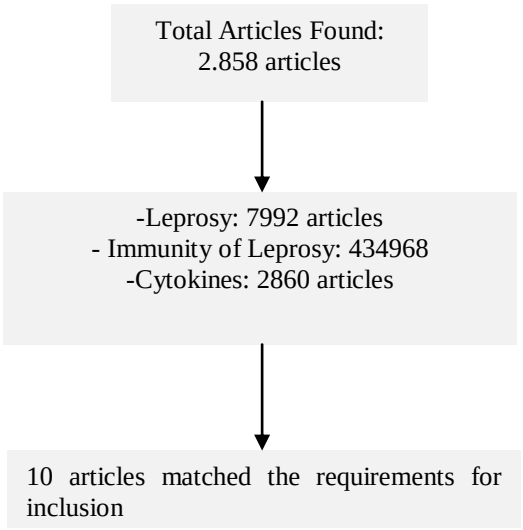
The immune response against *M. leprae* consists of innate and adaptive immune responses [4]. The innate immune system is activated by the pattern recognition receptor (PRR) which consists of Toll-like receptors (TLR) and NLR. The NLR functions to identify pathogens contained in the cytoplasm [8][4]. NOD-Like receptors (NLR) can activate caspase-1 and induce pro-inflammatory cytokines such as TNFα. IFNγ, IL-6 and IL-12. In cases of leprosis, cellular immunity plays a role, namely IFNγ and IL-12. IFNγ and other cytokines will promote/presented by IL-8 cytokines produced by macrophages, besides that IL-8 can also increase cytotoxic activity and proliferation of CD8+ T cells [9][4]. The purpose of writing this article is to discuss more deeply how the immune system fights bacterial infections, especially Mycobacterium leprae which causes leprosy.

2. Method

This research design is an identification of research journals within a period of 5 years, namely from 2018-2022. The research journals reviewed are those contain cytokines that play a role in Leprosy infection.

Article Selection Method

Several inclusion criteria in this study were a) articles reviewed in this study related cytokines that play a role in Leprosy; b) Using interleukin intervention that plays a role in Leprosy. The Exclusion criteria in this study were cytokines that play role in other than in Leprosy, and journals published before 2018.



The 1st International Innovation Technology Proceedings
Vol 1 No 1 (2023): October
E-ISSN: 3030-9948
https://iite-proceeding.poltekindonusa.ac.id

Article Search Method

How to find articles in this study is examined methodically, starting with selecting research topics and generating English keywords for journal searches. The database used is PUBMED, SCIENCEDIRECT to search for articles throughout the year, from January 2021 to December 2022. The keywords are in English used are "Leprosy", "Cytokine", and "Immunity of Leprosy". The next step is to identify the title of the article that best fits the research we want. Then, abstract identification and overall content analysis were completed to provide study findings that match the researcher's objectives.

Search results in Figure 1. Then the researchers filtered the relevant article titles and inclusion criteria, in order to obtain 10 appropriate articles.

Analysis studies

According to the researcher's objectivities. Pertinent literature and data gathered utilizing the method of random controlled trial (RCT).

3. Result and Discussion

Based on research that has been conducted by looking at various populations, there are 10 articles that meet the inclusion criteria. There are 7 cytokines that play role in Leprosys, such as TNF-α, IFN-γ, IL-10, IL-2, IL-37, IL-17, IL-21.

Each cytokines produces a different immune response against *M. leprae*. Differences in the immune response in the form of cytokines indicate the need for different treatment needs based on the type of cytokines in dealing with *M. Leprae.*

Based on the above data, the 7 cytokines have anti-inflammatory and pro-inflammatory roles. After further analysis, the 7 cytokines were differentiated based on the response of Th1 and Th2 cells. The difference in Th1 and Th2 cells responses helps in finding therapies both vaccines and drugs to determine the desired mechanism of action of the immune response so that theraphy can be on target, attacking intracellular bacteria.

3.1. Results

Berdasarkan hasil pencarian di database, ditemukan bahwa sitokin yang berperan dalam infeksi Lepra tertera dalam table 2.

Table 2. Cytokines that play a role in the Leprosy infection process.

Cytokines	Role	Reference
TNF-α	Pro-inflammatory cytokines	[10]; [11]; [12]
IFN-γ	Anti-inflamatory cytokines	[13]

IL-10	Anti-inflammatory cytokines	[14]; [15]; [17]
IL-2	Anti-inflamatory cytokines	[16]
IL-37	Anti-inflammatory cytokine	[17]; [16];
IL-17	Pro-inflammatory cytokines	[18]
IL-21	Anti-inflammatory cytokines	[19]

IL-10

Interleukin (IL)-10 is an anti-inflammatory cytokine secreted by Th2 cells and inhibits cytokine synthesis and proliferation of Th1 cells. The balance between IL-12 and IL-10-producing monocytes is important for the final outcome of the T-cell cytokine response. Th1 cells in humans are IL-10-secreting cells. The function of Th1 cells is heterogeneous, some function as pro-inflammatory and others as anti-inflammatory. Strong IL-12 expression and weak IL-10 expression in TT lesions occur due to local IFNγ release [19][14][15][17].

TNF-α (Tumor Necrosis Factor)

TNF-α is a key cytokine involved in the immune response against various pathogens. These cytokines are pro-inflammatory for macrophage activation and granuloma formation in preventing mycobacterial infection. TNF-α is an antagonist to IL-12 levels. TNF-α is actively produced by macrophages and polymorphonuclear (PMN) cells. *Mycobacterial lipopolysaccharide* (LPS), which is the main inducer of monocytes**,** can stimulate neutrophils to produce TNF-α. TNF-α is a cytokine that is important for the formation of granulomas, which are the basic pathological features of leprosy in the skin and nerves, as well as for the movement of leukocytes during inflammation. The increase in the TNF-α/IL-10 ratio plays a role in controlling mycobacterial invasion and replication. A higher TNF-α/IL-10 ratio is associated with a better prognosis.

TNF-α levels in the serum of leprosy patients will decrease after administration of MDT (multi-drug therapy) in accordance with the decrease in the number of bacteria. This decrease in cytokine production can be seen from the skin lesions of TT leprosy patients after MDT administration, but will remain high in untreated TT leprosy. LL/BL type leprosy that had been treated for six months did not show any significant changes. It should be emphasized that the defects in specific cellular immunity in LL patients are permanent and cannot be reversed with treatment.

Inflammation in RR occurs due to increased proliferation of T cells against *M. leprae* antigens, increased production of IL-1β, IL-2, TNF-α and IFN-γ, and decreased levels of IL-4, IL-5 and IL-10. This indicates an increase in the cellular immune response against *M. leprae*. TNF-α will increase by IFN-γ induction and autocrine mechanisms (autoregulation). These cytokines also play

an important role in the process of inflammation and damage to tissues and nerves through the induction of apoptosis.

The results of the study by Manandhar et al., showed that peripheral blood mononuclear cells from leprosy patients with untreated RR had significantly higher levels of TNF-α than leprosy patients without a reaction. Generally, IFN-γ and TNF-α in patients with RR decreased during steroid therapy, but TNF-α levels increased when the steroid dose was reduced. IL-10 levels also increased during the period of steroid therapy and were strongly associated with TNF-α levels. The results of another study by Faber et al., showed an increase in TNF-α in four out of seven leprosy patients with TNFα reaction plays an important role in the pathogenesis of ENL. The levels of this cytokine increase due to spontaneous release of TNF-α by peripheral blood mononuclear cells and stimulation of M. leprae cell wall components. No correlation was found between systemic symptoms and TNF-α levels. It can be concluded that TNF-α plays a role in leprosy reactions, both directly and synergistically with other cytokines. Recurrence of reaction episodes can occur due to other infections such as dental or periodontal abscesses, thereby increasing cytokines including TNF-α. High levels of IL-2 and TNF-α's are associated with relapse of borderline lepromatous (BL)/lepromatous (LL) to tuberculoid (TT)/borderline tuberculoid (BT) types. Whereas in TT/BT type leprosy that relapsed into BL/LL type, there was an increase in the production of Th2 cytokines (IL-4, IL-5, IL-6, IL-10). High IL-10 levels are also associated with reactivation.

IL-37

IL-37 plays a role in inhibiting the production of CXCL8, IL-8, and S100A7 in keratinocytes. Research by De Sousa et al., (2018) reported the results of immunohistochemical analysis showing very high expression of IL-37 in plaque psoriasis in humans. IL-37 plays a role in the immunosuppressive mechanism by modulating the activity of keratinocytes, endothelial cells, macrophages, and lymphocytes in the forms of TT and LL disease [16].

3.2. Discussion

***Leprosy* is a global disease**

The globally transmitted *Leprosys* proses a significant threat to developing countries, 80% found in Brazil, India and Indonesia New leprosy cases have been remarkably reduced by multidrug therapy (MDT) developed with the support of the World Health Organization (WHO) [21], but in 2019 around 200,000 cases were still reported from over 100 countries [5].

Cytokines-cytokines that play a role in *Leprosys* disease

The 1st International Innovation Technology Proceedings
Vol 1 No 1 (2023): October
E-ISSN: 3030-9948
https://iite-proceeding.poltekindonusa.ac.id

Two cytokines important for the infection of Leprosys are TNF-α and IFN-γ. The innate immune system is the first line of defense against *M. leprae* infection. Natural killer (NK) cells, cytotoxic T lymphocytes, and activated macrophages can destroy pathogens and then activate the adaptive immune system through the secretion of cytokines and antibodies. The innate immune response is modulated by the presence of antigen presenting dendritic cells, and the low virulence of *M. leprae* may preclude the development of the clinical manifestations of leprosy.

Regulation of inflammatory cytokines and chemokines can lead to the proliferation of T helper 1 (Th1) or T helper 2 (Th2) lymphocytes, which increase cellular or humoral immune responses against *M. leprae,* respectively. Cellular immunity is involved in the development of skin lesions, and humoral immunity is involved in the production of IgM antibodies to *phenolic glycolipids* (PGL-1), thus allowing bacillary spread.

In addition to being ineffective in preventing the development of the disease, the cellular immunity of individuals with tuberculoid disease also deteriorates, so that it is directly involved in the appearance of skin lesions. The humoral immunity of individuals who develop the lepromatous form of the disease, which is responsible for the production of IgM antibodies to PGL-1, provides no protection, allowing bacillary spread. The immunological response to *M. leprae* not only determines the course of the disease, but also determines the type of leprosy or leprosy that will manifest. Tuberculoid leprosy patients are able to limit the growth of the pathogen and have a strong T-cell response to *M. leprae.* It is characterized by the production of Th1 cell cytokines that form tuberculoid granulomas associated with the protective and destructive immunity of *M. leprae*. In contrast, lepromatous leprosy patients show a weak T-cell response *to M. leprae.* Lesions in lepromatous leprosy express Th2 cell cytokines (IL-4, IL-5, IL-6, IL-9, and IL-10), which play a role in antibody production, inhibition of macrophage function (macrophage granuloma formation), and suppression of SIS so that it allows intracellular bacteria to multiply [19]. The dynamics of the natural immune response in leprosy can be understood by knowing the relationship between *M. leprae* specific antibodies and the secretion of various cytokines (IFN-ϒ, IL-2, IL-5, IL-10, IL-6, TNF-α, and granulocyte macrophage colony- stimulating factor [GM-CSF]) in leprosy or leprosy patients. IFN-γ and TNF-α cytokines are immunoprotective, while IL-2 and IL-10 are immunosuppressive against *M. leprae* [19].

In the initial protection stage, non-specific mechanisms are mainly carried out by monocytes which act as phagocytic cells. In addition to monocytes, the response to infection also increases the production of neutrophils from the bone marrow. Neutrophil production is induced by CSF cytokines. Neutrophils phagocytize circulating microbes as well as microbes in the extravascular tissue and produce partial lysis. Neutrophils survive only a few hours, while circulating monocytes survive for up to 5 days. However, monocyte cells can migrate to the connective tissue and survive for several months as histiocytes [19].

Some of the bacteria that escape will join the monocytes in the bloodstream. As long as they are in monocytes, these bacteria can even replicate (Troyan horse phenomenon) and enter various organs. These stimulated monocytes differentiate into macrophages with high energetic activity, and are able to form epithelioid cells in TT-type leprosy and leprosy cells (Virchow cells) in LL-type leprosy. Activated macrophages in TT leprosy are also capable of phagocytizing intraneural bacilli. Macrophages also act as antigen presenting cells (APC) in both cellular and humoral immune responses.

Bacteria that emerge from the dead and ruptured monocytes will invade Schwann cells and enter phagocytic vacuoles (phagosomes), so that they can multiply and be protected from antibodies and macrophages. However, *M. leprae* can also leave its hiding place and enter the perineural tissue, resulting in the formation of epithelioid granulomas. Schwann cells do not have lysosomal enzymes to destroy bacteria, so *M. leprae* bacilli can survive for a long time [19][20].

4. Conclusion

Cytokines that play a role in *M. leprae* infection are TNF-α, IFN-γ, IL-10, IL-2, IL-37, IL-17, IL-21. Each cytokine will produce a different immune response against pathogens so that it can be used to perform both vaccine and drug therapy for *M. leprae* infection.

5. References

[1] M. Hernandez, T. Oliveira Fulco, R. Olmo Pinheiro, R. de Meirelles Santos Pereira, P. Redner, E. Nunes Sarno, U. Gazos Lopes, E. Pereira Sampaio, "Thalidomide modulates Mycobacterium leprae-induced NF-κB pathway and lower cytokine response", European Journal of Pharmacology, vol. 670, Issue 1, 2011, p. 272-279,https://doi.org/10.1016/j.ejphar.2011.08.046.

[2] C. A. Madigan, C. J. Cambier, K. M. Kelly-Scumpia, P. O. Scumpia, T. Y. Cheng, J. Zailaa, B. R. Bloom, D. B. Moody, S. T. Smale, A. Sagasti, R. L. Modlin, L. A. Ramakrishnan. "A

Macrophage Response to Mycobacterium leprae Phenolic Glycolipid Initiates Nerve Damage in Leprosy", Cell, vol. 24; 170(5):973-985.e10, 2017. doi: 10.1016/j.cell.2017.07.030. PMID: 28841420; PMCID: PMC5848073.

[3] I. Gusti Nyoman Darmaputra., N. Nyoman Tri Priliawati., Juliyanti., I. A. Diah Purnama Sari., L. Made Mas Rusyadi. "A Retrospective Study of Erythemanodusum Leprosum In Dermatology and Benereology Outpatient Clinic of Sanglah General Horapital, Bali-Indonesia", Journal of Global Pharma Technology, vol. 10;12, 2018.

[4] O. Suwarsa., H. Gunawan., P. Aji Achdiat. "Imunitas Bawaan pada Kusta: Hubungan Ekspresi Kaspase-1 dengan Interleukin-18 pada Pasien Kusta", Bandung Medical Journal, vol. 48, no. 3, 2016.

[5] Ministry of Health Repulic of Indonesia. "Prevalensi Kusta Pada Anak Tinggi, Temukan Kasusnya, Periksa Kontak dan Obati Sampai Tuntas", Direktorat Jenderal Pencegahan dan Pengendalian Penyakit. Avaliable in http://p2p.kemkes.go.id/pravalensi-kusta-pada-anak-tinggi-temukan-kasusnya-periksa-kontak-dan-obati-sampai-tuntas/, acces in Aug 21, 2023.

[6] M. Goto. "Pathology and classification" in Makino M, Matsuoka M, Goto M, Hatano K, penyunting. Leprosy science working toward dignity. Kanagawa: Tokai University Press; p. 118–23, 2011.

[7] N. Van der Wel., D. Hava., D. Haouben., D. Fluitsma., M. Zon., J. Pierson. "M. tuberculosis and M. leprae translocate from phagolysosome to the cytosol in myeloid cells", Cell, vol. 129, no. 7, p. 1287–98, 2007

[8] L. Franchi., T. Eigenbrod., R. Munoz-Planillo., G. Nunez. "The inflammasome a caspase-1 activation platform regulating immune responses and disease path pathogenesis". Nat Immunol. Vol. 10, no. 3:1–15, 2009.

[9] M. Sahoo., I. Ceballos-Olvera., L. Del Barrio., R. Fabio. "Role of the inflammasome IL-1β and IL-18 in bacterial infections". Sci World J. vol. 11:2037–50, 2011.

[10] R. Yuniati., F. Firdaus Munita., B. Dayana., F. Amalia. "Difference of Tumir Necrosit Factor (TBF-α) levels in Multibacillary Leprosy between Reverse Reaction and Non-Reverse Reaction Patients", Pakistan jjournal of Medical and Health Sciences, vol. 12, no. 3, 2018.

[11] D. Mitra. "A randomized controlled trial of prednisolone vs TNF-alfa inhibitor Infliximab in the management of type 1 lepra reaction in leprosy patients", International Journal of Infectious Diseases, vol. 101(1), no. 454, 2020.

[12] A. L. Cogen., E. Lebas., B. De Barros., et al. "Biologics in Leprosy: A Systematic Review and Case Report". The American Journal of Tropical Medicine and Hygiene, vol. 102(5):1131-1136, 2020. doi:10.4269/ajtmh.19-0616

[13] A. Edson Queiroz., N. I. Medeiros., T. Rafael Mattos., B. F. Pinto., A. M. Paula Carvalho., W. O. Dutra., F. C. Félix-Lana., R. C. Oliveira., J. A. S. Gomes. "CCL2 and IFN-γ serum levels as biomarkers for subclinical infection in household contacts of leprosy patients", Microbial Pathogenesis, vol. 150, 104725, 2021. https://doi.org/10.1016/j.micpath.2020.104725

[14]M. Tarique., H. Naz., C. Saini., M. Suhail., H. Shankar., N. Khanna., A. Sharma. "Association of IL-10 Gene Polymorphism with IL-10 Secretion by CD4 and T Regulatory Cells in Human

Leprosy", Front Immunology, vol 6, no. 11: 1974, 2020. doi: 10.3389/fimmu.2020.01974.

[15] D. Oktariana., I. Saleh., Z. Hafy., I. A. Liberty., E. M. Salim., L. Legiran. "The role of IL-10 in Leprosy: A Review", Indian Journal og Leprosy, vol. 94. P. 321-334, 2022

[16] J. R. de Sousa., M. Nacagami Sotto., J. A. Simoes Quaresma, "Leprosy As a Complex Infection: Breakdown of the Th1 and Th2 Immune Paradigm in the Immunopathogenesis of the Disease",Front. Immunol, vol. 8, 2017. https://doi.org/10.3389/fimmu.2017.01635

[17] I. Gusti Nyoman Darmaputra., L. Mas Rusyati., W. Riawan., A. Endaryanto., C. Rosita., S. Prakoeswa. "The Correlation between Neutrophil CD64, Interleukin-17 (Il-17), Interleukin-10 (Il-10) in Skin Tissue and Neutrophil CD64, Il-17 and Il-10 in Blood Circulation in Erythema Nodosum Leprosum (ENL) Patients", Proceedings of the 23rd Regional Conference of Dermatology (RCD 2018), pages 286-290, 2021. DOI: 10.5220/0008155802860290

[18] A. G. A. Farag., A. Z. Labeeb., A. N. A. Gerges., M. E. Elshaib. "Interleukin-17A in Egyptian leprosy patients: a clinical, genetic, and biochemical study", An Bras Dermatol, Vol. 97(6):735-741, 2022. doi: 10.1016/j.abd.2021.09.016. Epub 2022 Sep 21. PMID: 36153175; PMCID: PMC9582869.

[19] Sari., Amiruddin., A. Adam., Djamaluddin., Vitayani. "Peran Interlukin -2 (IL-2), Interlukin-10 (IL-10) dan tumor necrosis factor-α (TNF-α) pada penyakit kusta". MDVI, vol 40 No. I : 35-40, 2013.

[20] X. Illarramendi., E. Rangel., A. M. Miranda., A. C. Castro., G. O. Magalhaes., S.L.G. "Antunes.. Cutaneous Lesion Sensory Impairment Recovery and Nerve Regeneration in Leprosy Patients". Mem Inst Oswaldo Cuz; vol. 107(1), p. 68-73, 2012.

[21] World Health Organization. Global leprosy (Hansen disease) update, 2019: time to step-up prevention initiatives. Wkly Epidemiol Rec. 2020;95(36):417–440. [Google Scholar].