Research article

Comparison of interleukin-17 level in leprosy and non-leprosy patients at Dr. Muhammad Hoesin Palembang general hospital

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Key words: Leprosy, Interleukin-17, Patients.

Abstract

Leprosy is a chronic disease caused by an infection of Mycobacterium Leprae. Leprosy has several clinical types that correlate with the immune response. The study was conducted to analyze the differences in serum IL-17 levels between leprosy and non-leprosy patient in RSUP Dr. Muhammad Hoesin Palembang. Research design is case control. The study was conducted at Dr. Muhammad Hoesin Palembang General Hospital and IL-17 Examination was conducted at the Molecular Biology Laboratory, Medical Faculty of Sriwijaya University Palembang from January to February 2019. The case and control groups samples were 40 lepers and 40 medical personnel and paramedics who work at Dr. Muhammad Hoesin Palembang General Hospital and also patients family. The parameters studied were IL-17 levels, respondent status, clinical type of leprosy and respondent characteristics. Serum IL-17 is measured with ELISA. The average age of leprosy patient is 35 years, and non-leprosy is 36.5 years. The frequency of men (27) is higher in lepers and women (24) in non-lepers. MB patient (36) is higher compared to PB patient (4), and there are 19, 10, and 7 respondent of BL, LL, and BB patient respectively. And also there are 2 respondent of TT and BT patient. The median score of IL-17 levels for non-lepers are 47.86 pg/ml and for lepers are 102.86 pg/ml with p <0.05. Conclusion, there are significant differences in IL-17 levels in lepers and non-lepers at Dr. Muhammad Hoesin Palembang General Hospital.

Introduction

Leprosy is a chronic disease caused by infection of Mycobacterium Leprae and damage body organs including nerves and skin. This disease causes complex problems either physical, psychological, social, economic and cultural. The existence of leprosy has been around for thousands of years, but until now the disease is still a health problem throughout the world including Indonesia [1]. The incidence of leprosy in the world in 2015 are 210,758, and regionally, Southeast Asia has the highest number of case (156,118) followed by the Americas and Africa (28,806 and 20,004). Indonesia was the third highest in the world with 17,202 incidences in 2015 after India and Brazil (127,326 and 26,395). Globally, the incidence of leprosy has been decreasing, but in some countries such as Bangladesh, Congo, Ethiopia, India, and Indonesia the incidence reported to be increased. Prevalence of this disease in Indonesia is 15,920 in 2017, it is 0.70 cases / 10,000 population [2].

Leprosy has several clinical forms that correlate with different immunological patterns. The clinical manifestations of lepers vary from person to person, this is due to variations in the response of cellular immunity in each individual [8]. Leprosy is classified into several types, Ridley and Jopling in 1966, classified leprosy as a tuberculoid tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL) and lepromatous (LL), whereas World Health Organization (WHO) in 1996 divided leprosy into a paucibacillary leprosy (PB) with less than five skin lesions and multibacillary leprosy (MB) with more than five skin lesions or all patients with positive acid-fast bacilli (BTA) [3]. The types of leprosy show different immunological patterns. TT leprosy which is included in PB leprosy type has strong cellular immune, characterized by predominance of helper T1 - lymphocytes (Th1) cells and produces inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), gamma interferon (IFN-γ), interleukin six (IL-6), and IL-1 β, while LL leprosy which is included in MB leprosy type has fewer cellular immune. Its response dominated by Th2 cells and produce cytokines such as IL-10, tumor growth factor beta (TGF-β), IL-4 and IL-5, which induce suppressive responses, while other types provide a variety of immune responses [3, 4].

T cells contribute to the immunopathogenesis of the disease, recent T lymphocytes cell subpopulation in leprosy is helper T cell 17 (Th17). Th17 cells produce proinflammatory cytokines, that is interleukin 17 (IL-17). IL-17 together with other ILs such as IFN-γ participate
directly in the proinflammatory response and activate macrophages in carrying out microbicidal responses to Mycobacterium leprae. Macrophages are the main cells that play a role in microbicidal activity in leprosy [4]. IL-17 expression increases in TT type. In this case, IL-17 induces the production of TNF-α, IL-6, and induced nitric oxide synthase (iNOS), which can eliminate bacteria through the formation of oxide nitrite, while IL-17 expression is decreased in LL leprosy [4]. Defects of IL-17 secretion in leprosy can contribute to the development of multibacillary leprosy [3].

Some studies show controversial results regarding IL-17 levels in lepers and healthy controls. The results of these studies show that the average IL-17 level in lepers is significantly higher than non-leprosy, where BL type leprosy and reaction type 1 was higher than other types [5]. The average IL-17 level in leprosy was significantly lower than that of healthy controls, and based on the leprosy type showed a TT type higher than other types [3,6,7].

Material and method

Materials

Needle Vacutainer, Red lid vacutainer tube, Holder, Tourniquet, Alcohol swabs, Eppendorf tube, Gloves, Human Interleukin 17 Standard, Human Interleukin 17 Standard Diluent, HRP Conjugate Reagent, Sample Diluent, Chromogen Solution A, Chromogen Solution B, Wash Solution, Stop Solution, ELISA kit, all the materials were obtained from sigma Aldrich.

Types of research

This research is a case-control study that aimed to compare serum IL-17 levels between lepers and non-lepers in Dr. Mohammad Hoesin Palembang General Hospital.

Place and time of research

This research is conducted from January to February 2019 at Dr. Mohammad Hoesin Palembang General hospital, while IL-17 examination is carried out at the Medical Biology Laboratory, Faculty of Medicine, University of Sriwijaya Palembang.

Research Population

The case group population is all lepers treated at Dr. Muhammad Hoesin General Hospital Palembang from January to February 2019. The control group populations are medical staff and paramedics who work at Dr. Muhammad Hoesin Palembang General Hospital and the patients family. All the patients were agreed to be part of this research.

Research samples and ethical clearance

The study sample is the total population (lepers who were treated at Dr. Muhammad Hoesin General Hospital Palembang from January to February 2019). University of Sriwijaya committee was agreed and approved the ethical clearance of this research on January 2019.

Independent variable

Status of respondents and clinical types of leprosy.

Procedures

- Blood collection from all case and control groups, 40 patients each.
- Blood is inserted into the vacutainer tube.
- Blood is centrifuged at 2000 rpm for 20 minutes.
- The serum is transferred to the Eppendorf tube (RNA Nuclease-Free).
- The serum is stored in -20°C until it is examined in the Biomolecular laboratory of Sriwijaya University.
- Then, sample wells are prepared.
- Diluent samples were added as much as 40 µl into each sample well.
- Each sample is added 10 µl to the sample well according to the work map. Then the mixture sample is homogenized.
- The remaining solution in well 2 (standard 2) is removed 50 µl.
- Wells that contained standard series 1 to 8 are homogenized.
- 40 µl diluent samples are added into each sample well.
- Each 10 µl of sample is added to the sample well according to the work map. The mixture is homogenized.
- The well is closed with a seal plate and incubated for 30 minutes at 37°C.
- The solution is removed and washed 5 times with a wash solution. It is washed by filling each well with Wash solution using an auto washer. Finally, clean the remaining wash solution with aspiration or decanting method. Turn the dish over and clean it with a tissue.
- Conjugate reagent HRP is added 50 µl to each well, except blank wells, then it is homogenized.
- The well is closed with a new seal plate and incubated for 30 minutes at 37°C.
- The solution is discarded. Washing is repeated.
The well is closed with a new seal plate and incubated for 15 minutes at 37°C and should be protected from light.
- Stop Solution is added 50µl to each well (the color changes from blue to yellow).
- Standard optical density and samples are read by ELISA reader at a wavelength of 450 nm.
- Levels of IL 17 are calculated based on optical density values using the line equation formula.

**Result and discussion**

**Characteristics of respondents**
The study was conducted from January to February 2019 in Dermatovenerology department of Dr. Mohammad Hoesin General Hospital involved 40 leprosies and 40 non leprosy respondents. The characteristics of the respondents studied were categorized by age, sex, ethnicity, education, occupation, duration of illness and consumption of leprosy drugs. The characteristics of the respondents are shown in table 1.

<table>
<thead>
<tr>
<th>Respondent characteristics</th>
<th>Leprosy patient (40)</th>
<th>Non-leprocy patient (40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average (Interdisciplinary perspectives on infectious diseases)</td>
<td>35</td>
<td>36.5</td>
<td>0.584 *</td>
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<tr>
<td>Group of age</td>
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<td>18-40</td>
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<td>26</td>
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<tr>
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<td>&gt; 60</td>
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<td>2</td>
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</tr>
<tr>
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<tr>
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</tr>
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<td>6- 10 years</td>
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</tr>
<tr>
<td>&gt; 10 years</td>
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<tr>
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</tr>
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<td>MB &gt; 12 months</td>
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</table>

Description:
* = T-independent test, ** = Pearson Chi Square test, *** = Kolmogorov Smirnov test
Distribution of leprosy and non-leprosy patients based on clinical type
Characteristics of people affected by leprosy are classified according to the clinical type of leprosy. The clinical type group was then divided into two criteria, WHO and Ridley Jopling criteria. WHO criteria are divided into two, paucibacillary (PB) and multibacillary (MB). Ridley Jopling's criteria are divided into 5 criteria namely tuberculoid (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL), and lepromatous (LL). Distribution of respondents based on these criteria is shown in figure 1.

Serum IL-17 levels in lepers and non-lepers
Figure 2 shows that the Median of IL-17 level in leprosy patients is higher (102.86 pg/ml) than non-leprosy patients (47.86 pg/ml). The concentration range of IL-17 levels in lepers are 71.86 pg/ml to 117.86 pg/ml and in non-leprosy IL-17 levels are 30 pg/ml up to 59 pg/ml. The purpose of this study is to find a comparison of IL-17 levels in lepers and non-lepers. To answer the purpose of the study, the mean value of L-17 levels are tested in lepers and non-lepers. Before a test is done, the IL-17 level data obtained is tested to find out the normal distribution of data. SPSS program is used for data normality test along with the Shapiro Wilk test because the number of study samples is less than 50. The results of the normality test for IL-17 levels in lepers and non-lepers show that the data are not normally distributed (p-value <0.05).

Figure 1. Distribution of leprosy patients based on clinical types of WHO criteria and Ridley Jopling.

Figure 2. Graph of IL-17 levels in lepers and non-lepers.

*: Mann Whitney test
Serum IL-17 levels in leprosy patients are based on clinical types of WHO criteria and Ridley Jopling

Figure 3 shown for the WHO clinical criteria, the median IL-17 level between the PB and MB types is not much different, while the median IL-17 level in the PB type is slightly higher (103.22 pg/ml) using the MB type (102.86 pg/ml). In the clinical type criteria, Ridley and Jopling suggested that the BB type had a higher median IL-17 level (110 pg/ml) than other types and BT type had a lower level (92.15) than different models. The minimum and maximum values between PB and MB types are the same, namely 72.86 pg/ml and 117.86 pg/ml, for Ridley Jopling criteria the range of minimum and maximum values is 72.86 pg/ml to 117.86 pg/ml.

**Distribution of leprosy and non-leprosy patients based on cut-off point value of interleukin-17 level**

The cut-off point value of serum IL-17 levels in this study is determined with MedCalc program. Based on the program, the cut-off point value is obtained at levels greater than 59 pg/ml. IL-17 levels which are lower or equal to 59 pg/ml grouped as “not elevate” and if higher than 59 pg/ml then it is grouped as “elevate”. Distribution of non-lepers and lepers based on the cut-off point value of IL-17 levels can be seen in the figure 4.

![Figure 3. Graph of median IL-17 levels in leprosy patients based on the clinical type of WHO criteria, Ridley Jopling and leprosy reactions.](image)


*: Mann-Whitney test

**: Kruskal Wallis test

![Figure 4. Distribution of IL-17 levels based on the cut-off point value.](image)
Discussion

The distribution of respondents by age in this study is in line with the research conducted by Abdallah, et al. who had his research at the Elq'aa Cairo Dermatology and Leprosy Hospital in 2013. In Abdallah's study, et al. They found that the average age of lepers are 35 years and non-lepers are 36 years old [3]. The results of this study are similar to the descriptive research of Bhat and Chaitra who researched in South India in 2013 and research by Nalamada et al. who conducted their research in Hyderabad, Telangana, India in 2016 to 2017. Bhat and Chaitra reported that prevalence of leprosy is more in the 16-50 age group with 33 respondents from 46 patients [9]. Nalamada et al. have found out that from 96 lepers, the frequency of leprosy is more prevalent in the age of 20 to 40 years (50%), followed by patient in the age of more than 40 years (33%), and the lowest frequency of leprosy is patient in the age of less than 20 years (16.6%) [10].

The results show that the incidence of leprosy is more common in male (27) than female (13). The results of this study are similar to the previous study such as the Nalamada et al. Study which conducted in Hyderabad, Telangana, India in 2016 to 2017 and a study by Nabilla et al. Which conducted on the Kediri Leprosy Hospital in January and February 2012. The two studies are obtained that the majority of lepers are male (75%) compared to female (25%) with 3: 1 ratio [10, 11]. Abdallah's research, et al. who conducted their research at the Hospital of Dermatology and Lepra Elq'aa Cairo in 2013 found that out of 43 leprosy patients there were 27 respondents who are male (62.8%) and 16 patients female (37.2%). Attia et al. who conducted their research at The Elq'aa Hospital of Dermatology and Leprosy Cairo in 2014 show the majority of lepers are male (27) compared to female (16) [3,12].

Characteristics of respondents based on drug consumption showed that most of the leprosy patients (19) had received MDT MB treatment with a span of 0-12 months and a small group of respondents had not received any treatment (2). Leprosy patients who have not received any treatment are considered as new cases. Treatment is aim to break the chain of transmission, if the organism is eliminated, the source of transmission from people affected by leprosy to others, especially MB, can be cut off [1]. It takes years for Lepers who get treatment, to reach IB 0 status. Mycobacterium Leprae will disappear in a few months in BB type, one or two years in BL type, whereas in LL patients the time needed for Mycobacterium leprae to disappear from the skin is 6-10 years [13]. Irregular treatment will cause resistance to MDT, and result in symptoms of the disease settling or worsening. PB patients will take MDT medicine for 6-9 months while MB patients for 12-18 months [1]. In this study, there are leprosy patients who received 24 months MDT MB, 24 months full MDT MB given for patients with a bacterial index of more than four [14].

The results of the study on the distribution of leprosy patients based on clinical types show that MB is the clinical type with the most distribution of leprosy patients (36) on WHO criteria. The results of this study are the same as the results of a study by Nabilla et al. In Kediri Leprosy Hospital in 2012 which received the most leprosy patients with MB type, 110 patients (91.67%), while only 10 patients of PB type (8.33%). The results of the study of Nalamada et al. in Hyderabad Telangana India in 2016 to 2017 also showed a larger number of MB type (53%) compared to the PB type (47%) [10]. This research data is the same as the data released by the Indonesian Health Profile Data And Information in 2017. It shows that the number of MB patients is greater (89.6%) compared to PB patients (10.4%) [15].

Based on Ridley Jopling criteria, BL type has the highest distribution (19) while TT and BT types have the lowest distribution (2). The results of this study are similar to the research of Dewi and Oemat who conducted their research at Sanglah General Hospital Denpasar in 2016, in his study the frequency of BL type is the highest (20), and TT type is the lowest TT (2) [16,17]. The results of this study are different the study of Nalamada et al. and Bhat and Chaitra, in the Nalamada et al. Study, BT type has the highest frequency (33%), and TT type has the lowest frequency (9%). Bhat and Chaitra studies show that BT type has the highest frequency (16) and LL type has the lowest frequency (2) [10, 18].

The difference in the number of types of leprosy in each study depends on the location where the study is conducted [16]. MB type leprosy is more prevalent than PB type because MB type is the main source of infection (more easily transmitted) than type PB [1]. PB type leprosy includes TT and BT, while the MB type includes BT, BB, and BL. MB type indicates an ineffective cellular immune response and slow diagnosis and treatment. Leprosy that is not diagnosed and treated at an early stage, the cellular immune response will determine the development of the disease. If the cellular immune response can effectively eliminate or control infection in the body, lesions heal spontaneously or develop PB type leprosy. If the cellular immune response is ineffective or weak, Mycobacterium replication is uncontrolled and produces MB type leprosy [19].

The results of the study on the distribution of leprosy patients based on the presence or absence of leprosy reactions showed that from 40 lepers there are 14 lepers who had a leprosy reaction. The leprosy reaction that occurred is a type II reaction or also called Erythema Nodosum Leprosum (ENL) reaction. Based on the clinical type of WHO criteria and Ridley Jopling Criteria, it showed that all PB (WHO criteria), TT and BT patients (Ridley Jopling criteria ) did not experience any ENL reactions. ENL reaction only occurs in MB patients
(WHO criteria), BL and LL patients have a higher frequency (8 and 5) than BB patients (1).

The results of the distribution of non-leprosy patients based on contact history with patients according to WHO and Ridley Jopling clinical criteria showed that most of the non-leprosy patients (22) had contact with PB and MB type patients and only 2 patients had contact with PB type. Respondents who had contact with PB and MB type are medic personnel and paramedics. The results of this study are different from Neto et al. Study in 2014 which showed that out of 10 non-leprosy patients there were 7 patients who had contact with PB patients and 3 patients who had contact with MB patients [20]. This difference can be caused by the majority of the respondents who are non-lepers are medical staff and paramedics who carry out their work activities in contact with leprosy patients with various clinical types, while in the previous study the respondents were individuals living with lepers (home contact ladder), so that contact is limited to certain clinical type of leprosy.

The results showed that IL-17 levels in lepers were higher (102.86 pg/ml) than in non-leprosy patients (47.86 pg/ml) and there are significant difference in the mean value of IL-17 levels between lepers and non-lepers. The results of this study are the same as the research conducted by Chaitanya et al in New Delhi India on 181 lepers who had not received treatment and 94 non-lepers. This study showed IL-17 levels in leprosy patients are significantly higher (median 131.5 pg/ml up to 197.91 pg/ml) compared to non lepers (median 102.3 pg/ml) (P value <0.05). Santos et al study in Brazil on 51 leprosy patients and 23 non-contact households showed that IL-17 levels in leprosy patients were significantly higher (mean value 38.5 pg/ml up to 47.2 pg/ml) compared to household relatives (mean value 37.3 pg/ml) (P value <0.02) [21, 22].

The difference research results can be due to the majority of lepers have received MDT treatment whereas in previous studies all lepers were new cases who had not received any treatment. Treatment of MDT changes the levels of cytokines. Cytokine production in leprosy patients is due to the stimulation of immune cells by antigen from Mycobacterium leprae and treatment can reduce these cytokine levels found in non-infected individuals [23]. Mobasher et al. study show that after 1 year of MB patients treatment levels of cytokines significantly decreased, but the levels remained high in healthy controls [24]. Increased of IL-17 levels in all lepers compared to non-lepers showed that Mycobacterium Leprae stimulated IL-17 production [21]. This increase can be caused by the activation of the cellular immune response by MDT. MDT can reduce the viability of mycobacterium leprae and its morphological integrity. In vitro trials revealed that live mycobacterium leprae is a suppressor of the immune response, while dead mycobacterium leprae is a trigger for the cellular immune response [20]. Rifampicin in MDT is bactericidal, it increases massive destruction of Mycobacterium Leprae and releases many antigenic fractions that cause inflammatory reactions [24]. This theory was proven in studies that PB type leprosy patients who had not been given MDT indicate low IL-17 levels and after MDT administration IL-17 levels are increased. MB patients show high IL-17 levels before and after MDT treatment [23]. Neto et al. study in 2014 showed a significant increase in IL-17 levels (P <0.05) after 2 months of treatment in MB lepers, whereas in PB patients there are no significant differences before and after treatment [20]. Another study conducted by Neela et al. in India in 2016 showed low IL-17 levels before MDT treatment than healthy controls and increased after MDT treatment, where 12-month MDT treatment had higher IL-17 levels compared to 6 months MDT treatment [21]. IL-17 mediates an inflammatory reaction by recruiting neutrophils and activate macrophages. High inflammatory response of these cells is very important for self immunity to pathogens, while this uncontrolled inflammatory response from IL-17 can lead to autoimmunity and inflammatory conditions that lead to pathogenesis [23]. In leprosy, IL-17 activate macrophages by inducing the production of iNOS, which will induce changes in arginine and produce NO which will play a role in the destruction of bacteria. Another role of IL-17 in leprosy is to inhibit production (NGF) which will lead to severe nerve lesions [4, 19].

Previous research showed that IL-17 levels in lepers are significantly lower than healthy controls [3, 6, 7]. Low IL-17 levels in the study occurred due to suppression of the immune response by Mycobacterium Leprae. This condition is obtained due to the inhibition of SD which will disrupt T cell induction and T cell responses. The presence of IL-10, IL-4 and IFN-γ will interfere Th17 cell differentiation thereby reducing IL-17 production [19]. Blocking IL-10, IL-4 and TGF-β will result in a reversal of the effector immune response of IL-17, indicating that by eliminating the effect of suppressive cytokines can restore the IL-17 immune response [24]. The results show that IL-17 levels between PB and MB types are slightly different, where the median value of IL-17 levels in PB type is slightly higher (103.22 pg/ml) than MB type (102.86 pg/ml). Referring to Ridley and Jopling criteria, it showed that BB type has a higher median value of IL-17 level (110 pg/ml) than the other type and BT type have the lowest median value of IL-17 level (92.15) compared to the other types. Test results from WHO and Ridley Jopling criteria showed no significant difference in IL-17 level between PB and MB patients as well as between TT, BT, BB, BL and LL patients. The results of this study are similar to Abdallah et al. study in Cairo in 2013 which showed that IL-17 levels in PB patients are slightly higher (median value 20 pg/ml) than MB patients (median 19 pg/ml) and there are no
significant differences in the mean value of IL-17 levels between PB and MB patients (P value 0.989> 0.05) [3]. The results of this study are different from Santos et al. in Brazil in 2017 which showed that IL-17 levels in PB patients are higher (mean value 47.2 pg/ml) compared to the MB patients (mean value 38.5 - 40, 5 pg/ml) and there is a significant difference in the mean value of IL-17 level between PB and MB patients (P value <0.05) [22]. Immunological responses to invading pathogens can determine the clinical manifestations of infection in the host. This condition is found in leprosy, where the cytokine pattern determines the spectrum of the disease. Leprosy is the first disease classified according to cytokine profiles. The immunological spectrum correlates closely with the level of immunity mediated by T cells [24]. The PB leprosy type consisting of tuberculoid type (TT and BT) displays a low bacterial burden caused by an effective cellular immune response mediated by inflammatory cytokines such as IFN-γ, TNF-α, IL-17, IL-6, and IL-1β. In this type, there will be an increase in levels of inflammatory cytokines [20]. MB type which also BB, BL, and LL type displays a weak cellular immune response and a strong humoral immune response and is mediated by anti-inflammatory cytokines such as IL-4, and IL-10, higher Treg cell expression and high bacterial load [3, 4]. Immunologically unstable borderline forms. In these groups, there is a gradual decline in cellular immune response from BT to BL, which is inversely correlated with an increase in bacterial load [20]. IL-17 expression increased in PB and TT types and the MB and BL and LL types decreased IL-17 expression. Increased expression of IL-17 will induce nitric oxide synthase (iNOS), which can destroy bacteria through the formation of oxide nitrite [4]. In this study there were no differences in IL-17 levels between each clinical type of leprosy, this condition could be caused by small sample size and treatment being carried out by lepers, where treatment increases the inflammatory reaction activated by inflammatory cytokines by IL-17. This occurs in all clinical spectrums, indicates an increase in the cellular immune response. Increased of IL-17 levels in lepers is needed to eliminate the Mycobacterium Leprae. Thus IL-17 plays a protective role in leprosy [20].

Conclusions
In conclusion IL-17 was higher in leprosy patient than in non-leprosy patients. And the distribution of leprosy patient is spread in all types. In WHO criteria, MB type has more frequency (36) than the PB type (4). In Ridley Jopling's criteria, the highest frequency leprosy patients is in BL type (19), followed by LL and BB types (10 and 7) and the lowest frequency occurred in TT and BT types (2). The median value of IL-17 level for non-leprosy patients is 47.86 pg/ml. The median value of IL-17 level in lepers is 102.86 pg/ml. There are significant differences in IL-17 levels in lepers and non-lepers in Dr. Muhammad Hoesin Palembang General Hospital.

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