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DIFFERENCES IN INTERFERON GAMMA LEVELS IN TREATMENT OF TUBERCULOSIS IN INTENSIVE PHASE AND ADVANCED PHASE

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Abstrak

Tuberkulosis (TBC) adalah penyakit menular kronis yang disebabkan oleh Mycobacterium tuberculosis complex (MTBC). Obat anti tuberculosis yang diberikan kepada penderita TBC aktif terdiri dari 3 atau 4 kombinasi. Pengobatan penyakit tuberculosis dibagi menjadi pengobatan fase intensif (2 minggu) dan fase lanjutan (16 minggu / 4 bulan). Interferon gamma (IFN γ) adalah suatu protein yang termasuk dalam keluarga sitokin yang berperan dalam eliminasi bakteri MTB melalui mekanisme cell-mediated immunity. Tujuan penelitian ini yaitu untuk menganalisa perbedaan kadar interferon gamma pada pengobatan tuberculosis fase intensif dan fase lanjutan. Metode penelitia ini merupakan penelitian observasional analitik dengan rancangan potong lintang (cross sectional study). Desain penelitian digunakan adalah randomized post test only control group design. Data dianalisis dengan menggunakan uji kruskal wallis dengan hasil uji statistik diperoleh nilai p 0,033 (> 0.05) berarti ada perbedaan kadar IFN γ pada pengobatan tuberculosis fase intensif dan fase lanjutan.

Kata Kunci *Tuberkulosis, Obat Anti Tuberkulosis, Interferon gamma (IFN γ)*

Abstrak

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis complex (MTBC). Anti-tuberculosis drugs given to active TB sufferers consist of 3 or 4 combinations. Tuberculosis treatment is divided into intensive phase treatment (2 weeks) and continuation phase (16 weeks / 4 months). Interferon gamma (IFN γ) is a protein belonging to the cytokine family which plays a role in eliminating MTB bacteria through a cell-mediated immunity mechanism. The aim of this study was to analyze differences in gamma interferon levels in the intensive phase and advanced phase of tuberculosis treatment. This research method is an analytical observational study with a cross-sectional design (cross sectional study). The research design used was a randomized post test only control group design. Data were analyzed using the Kruskal Wallis test with statistical test results obtained with a p value of 0.033 (> 0.05), meaning there was a difference in IFN γ levels in the intensive phase and advanced phase of tuberculosis treatment.

Kata Kunci Tuberculosis, Anti-tuberculosis drugs, Interferon gamma (IFN γ)

1. INTRODUCTION

The Mycobacterium tuberculosis complex (MTBC) consists of causative agents in a wide range of hosts tuberculosis and is responsible for over 10 million annual infections globally. They are rod-shaped, acid-base-fast, aerobic, slow-growing intracellular pathogens that destroy phagosomal cells to maintain and evade the immune system (Zhang et al., 2022).

Pulmonary TB cases dominate more than extra-pulmonary TB at the global level by 84 percent. Pulmonary TB is transmitted through saliva or phlegm that contains MT. On the other hand, extra- pulmonary TB is generally not contagious. However,

tuberculosis is generally an infectious disease and one of the top ten causes of death globally, among other infectious diseases (Andini & Oktora, 2022). Indonesia ranks second in the world as the country with the highest number of TB sufferers after India.Pulmonary TB sufferers are in developing countries around 80% with 25% mortality rate or 1.7 million peryear and 75% of TB sufferers are productivegroup (15-55 years old) (Nopita et al., 2023).

Bacteria that have been inhaled will survive in the alveolar lobes. The body's immune system will respond with an inflammatory reaction. The reaction of phagocyte and lymphocyte cells will cause a buildup of exudate in the alveoli tissue so that bronchopneumonia can occur. This initial infection generally occurs within two to ten weeks after exposure to the bacteria. Mycobacterium tuberculosis granulomas can persist for years in healthy individuals with latent tuberculosis. The granuloma will become necrotic so that pathogens cannot be controlled and proliferate massively in the core of the lesion. Rupture of the lesion will result in pathogens entering the bloodstream and can infect other organs. The latent state of TB changes to active TB and the patient becomes infectious (Putri, 2023).

Treatment for tuberculosis patients takes quite a long time, namely around 6 to 9 months. Anti-tuberculosis drugs (OAT) are drugs given to tuberculosis patients which can be divided into several lines. First-line OAT treatment itself consists of Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA), Ethambutol (EMB) and Streptomycin (S). There are also three types of TB treatment based on the explanation, namely categories 1, 2 and children. Category 1 TB treatment is intended for newly diagnosed clinical, bacteriological and extra-pulmonary patients with the 2HRZE/4HR treatment regimen. OAT is provided in the form of KDT (Fixed Dose Combination) and also in separate form. Tuberculosis treatment is divided into two stages, namely the intensive stage (H/R/Z/E) and the advanced stage (R/H). The next stage of treatment is aimed at killing dormant or surviving tuberculosis bacteria. This dormant germ, if not handled properly, can cause recurrence in tuberculosis patients (Fortuna et al., 2022).

Tuberculosis treatment will be optimal if supported by good immunity because Mycobacterium tuberculosis is a facultative intracellular bacterium which has the ability to live in phagocytic cells. These bacteria can hide from antibodies produced by the body, so eliminating them must be done through cellular immunity (Takdir et al., 2018). The protective role of IFN-γ in tuberculosis is well known, especially in specific T cell immunity antigens. Production of IFN-specific mycobacterium antigens in vitro can be used as a marker of TB infection (Bastian et al., 2020).

IFN-γ plays an important role in eliminating Mycobacterium tuberculosis. Interferon Gamma strengthens the phagocytic potential of macrophages infected with M.Tb, namely by stimulating the formation of phagolysosomes. Interferon Gamma also stimulates the formation of free radicals which can destroy M.Tb components. Interferon Gamma will stimulate macrophages containing TB germs to increase reactive nitrogen intermediate (RNI) which is needed to destroy TB germs (Setiawan & Nugraha, 2016).

Based on this description, researchers are interested in conducting research on the differences in interferon gamma levels in treatment of tuberculosis in intensive phase and advanced phase.

2. RESEARCH METHOD

This research is an analytical observational study with a cross-sectional design (cross sectional study). The research design used was a randomized post test only control group design. This research consisted of 2 groups. Group 1 suffers from intensive phase TB, group 2 suffers from advanced phase TB. The number of samples in this study was 15 for each group.

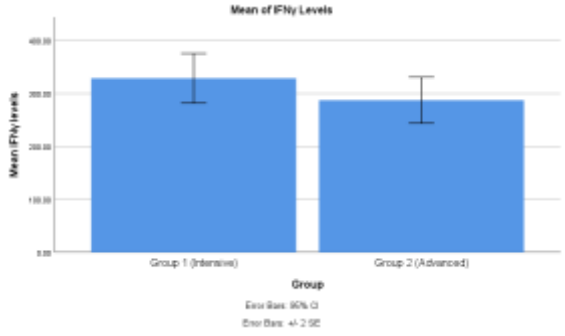
3. RESULTS

The data analysis test was used to determine the differences in interferon gamma levels in treatment of tuberculosis in intensive phase and advanced phase was *kruskal wallis*.

Table 1. Mean and standard deviation (SD) of IFN-γ levels

Group	Mean±SD
Group 1	328.77±91.16
Group 2	287.30±84.39

Based on table 1, it was shown that the mean in group 1 was 328.77 pg/mL, he mean the average in group 2 was 287.30. These differences can be observed in the graph below:



Tabel 2. Analysis of mean difference test for IFN-γ levels

Variabels	Group	P Value
IFN-γ levels	Group 1 Group 2	0.033

Based on table 2, the results of the analysis of the mean difference in IFN-γ levels with a value of p = (0.033) means there is a difference between the intensive group (group 1) and the advanced group (group 2).

4. DISCUSSION

Based on the results of statistical tests, the p value of 0.033 (> 0.05) means that there is between the intensive group (group 1) and the advanced group (group 2). A similar study was also conducted by Sinaga & Tarigan, 2022 which stated that Interferon-gamma level was significantly higher in PTB patients compared to healthy control (p = 0.024). Mean ± SD interferon gamma level was 317.2 ± 201.97 pg/ml in PTB patients and 213.5 ± 86.43 pg/ml in healthy control. Acid fast bacilli (AFB) positivity was significantly associated with interferon gamma level (p<0.001). Interferon gamma level in TB patients with AFB 1+ was 503.22 ± 146.15 pg/ml, AFB 2+ was 337 ± 81.61 pg/ml, and AFB 3+ was 88.27 ± 51.32 pg/ml. A similar study was also conducted by Pai et al., 2007 changes in IFN-γ responses over time were highly inconsistent some individuals showed increases, while others showed decreases or no changes. Although the average IFN-γ levels decreased slightly during treatment (not significant).

In this study there was a decrease in IFN-γ levels in group 2 because that T-cell IFN-γ responses to Mycobacterium tuberculosis-specific antigens decline as disease activity diminishes with tuberculosis (TB) treatment has generated interest in the IFN-γ (Chee et al., 2010). The use of antibiotics also causes a decrease in IFN-γ levels such as beta lactam antibiotics (Berns et al., 2022). Healthy people have lower levels of IFN-γ compared to TB patients, whereas in TB sufferers IFN-γ is significantly higher, increased levels of IFN-γ indicate a protective immune response against Mycobacterium tuberculosis infection (Hussain et al., 2010).

IFN-γ is one of the cytokines that plays the most role in macrophage activation and has an important function in eliminating Mycobacterium tuberculosis in the body, mainly produced by CD4 T cells, apart from that, CD8 T cells are also needed to increase the production of IFN-γ which provides protection when infected by Mycobacterium tuberculosis. IFN-γ strengthens the phagocytic potential of macrophages by stimulating phagolysosome fusion and stimulating the formation of free radicals that

can destroy Mycobacterium tuberculosis (Prihantika et al., 2019).

T helper-1 (Th1) cells play an important role in the body's defense system, especially in dealing with intracellular bacterial infections. One of the cytokines produced by Th1 cells is IFN-γ which plays an important role in eliminating Mycobacterium tuberculosis bacteria. Gamma interferon is tasked with strengthening the phagocytic potential of macrophages infected with Mycobacterium tuberculosis bacteria, namely by stimulating the formation of phagolysosomes. Gamma interferon also stimulates the formation of free radicals to destroy components of the Mycobacterium tuberculosis bacteria, namely DNA and bacterial cell walls (Widjaja et al., 2010).

IFN-γ will activate a number of signaling pathways and transcription factors, especially the most important in this case is STAT1, while signals from Toll like receptor (TLR) and CD40 will activate the transcription factor NF-κB and activation protein 1 (AP-1). This transcription factor will stimulate the expression of a number of enzymes in macrophage phagolysosomes, including: the phagocyte oxidase enzyme which will induce the production of reactive oxygen species (ROS); inducible nitric oxide synthase (iNOS), which stimulates nitric oxide (NO) production; and lysosomal enzymes. These various substances will destroy microbes that have been digested in the vesicles and are also responsible for the microbicidal function played by activated macrophages. IFN-γ also stimulates the production of antibody isotypes that will activate complement and opsonize bacteria for phagocytosis, thus helping the effector function of macrophages (Wahyuniati, 2018).

Several days postinfection, the adaptive immune response to TB is optimally activated, where CD4+ and CD8+ effector T-cells traffic to the lungs where they produce IFN-γ. At this stage, the concentration of IFN-γ would be ten times higher compared to that of type I IFNs. Many studies have shown that IFN-γ driven Th1 responses are crucial for the immune response in Mycobacterium tuberculosis infection. Since Mycobacterium tuberculosis is a pathogenic intracellular microorganism, Th1 type cytokines play a major role in stimulating cell-mediated immune responses for the development of host protection. Under these conditions, IFN-γ becomes the predominant immunomodulatory regulator by recruitment of T-cells, induction of expression of MHC class II molecules, augmentation of APCs, and control of Mycobacterium tuberculosis growth (Chin et al., 2017).

5. CONCLUSIONS

There was a difference between the intensive group (group 1) and the advanced group (group 2).

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