

# Pharmacokinetic Profile of Isoniazid and Acetylator Status in Patients with Systemic Lupus Erythematosus: Implications for Tuberculosis Prevention Therapy in Indonesia

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**Introduction:** Systemic Lupus Erythematosus (SLE) is a chronic autoimmune inflammatory disease with a high risk of tuberculosis (TB) infection, especially in those living in TB-endemic areas. Isoniazid (INH), an anti-tuberculosis drug, is recommended as preventive therapy in TB susceptible groups, however, its use in SLE is still controversial. SLE patients are more likely to have compromised liver function which can influence the kinetic of INH. The aim of the study was to explore the pharmacokinetic profile of INH and acetylator status in SLE patients.

**Methods:** This was a descriptive observational study with a purposive sampling technique, including adult female SLE at Dr. Hasan Sadikin Hospital Bandung, conducted in January - August 2023. Inclusion criteria were SLE patients in remission with no TB infection; whereas the exclusion criteria were INH allergy, liver or kidney disorders, pregnant or lactating patients, and malignancy. Pharmacokinetic data was collected from six blood collection time points (0, 1, 2, 3, 4, and 8 hours) after 10 days of daily INH 300 mg administration on an empty stomach.

**Results:** In total, 20 female SLE patients were included. The  $C_{max}$  value was 8.73 (2.55–18.27) mg/L and  $AUC_{0-24}$  was 28.01 (8.82–79.40) mg.h/L.

**Conclusion:** In terms of pharmacokinetic features, preventive isoniazid (INH) daily use of 300mg in SLE is sufficient to provide the prospect of protection from TB. These findings suggest that INH prophylaxis may be a viable strategy for TB prevention in SLE patients, warranting further investigation into long-term safety and efficacy.

**Keywords:** pharmacokinetics, INH, SLE, tuberculosis, acetylator status

## Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease, of which the cause remains unclear. This condition predominantly impacts women more than men as this is reinforced by epidemiological study data. The incidence of adult SLE in Indonesia is 14,828 for women and 2619 for men.<sup>1</sup> The clinical manifestations and disease course of SLE are complex and diverse in each individual.<sup>2,3</sup> Comprehensive effort in the accuracy of SLE diagnosis, therapy, prevention, and management of complications is highly needed. Infection is one of the most common complications in SLE patients and is one of the leading causes of death in SLE patients.<sup>4-6</sup> Disease activity, long-term use of immunosuppressant drugs, and environmental factors variably affect SLE patient's immunity and susceptibility to infection.<sup>4-6</sup>

Tuberculosis (TB) infection is among the most common infections in SLE patients, especially those living in endemic areas.<sup>5</sup> According to the World Health Organization (WHO) data, Indonesia is the second highest TB endemic country

globally, and the growth of TB cases, with or without SLE, in Indonesia from 2015 to 2019 increased significantly by approximately 69%.<sup>7</sup> Various studies have reported that SLE patients are 5–60 times more susceptible to contracting TB than the general population.<sup>5,8,9</sup> Similarly, our previous data has reported that 11.4% of 813 SLE patients developed TB.<sup>10,11</sup> The incidence of TB in SLE patients in Indonesia is 48.5/1000, which is the highest among other TB-endemic countries.<sup>10</sup> SLE and TB interact in complex and reciprocal ways, which can worsen the condition of SLE patients and even increase SLE morbidity and mortality.<sup>5,9,10</sup> These conditions are the basis of consideration for TB preventive therapy in vulnerable groups such as SLE. However, the provision of therapy for TB prevention in SLE is still a matter of debate because the results are inconclusive.<sup>12,13</sup>

Isonicotinic acid hydrazide, also known as Isoniazid (INH), is a first-line anti-mycobacterial agent or anti-tuberculosis drug (ATD) that is used in combination with other first-line ATDs for TB treatment and can be used as a single therapy for TB prevention.<sup>14,15</sup> There is still insufficient data to support ATD administration in groups with comorbidities; ATD-related studies have only involved Human Immunodeficiency Virus (HIV) and Diabetes Mellitus (DM) groups. Since its discovery, INH is still the drug of choice recommended by the WHO for TB preventive therapy in latent TB patients and TB-prone groups such as patients with HIV.<sup>16</sup> The consideration of administering INH as the preferred TB preventive therapy in SLE patients is due to the successful application of INH for TB preventive therapy in HIV patients and the potential adverse effects of other ATDs, such as rifampicin. Rifampicin can induce various enzymes in metabolic pathways, especially those involving the cytochrome-P450 system, reducing serum concentrations of several drugs, including various corticosteroids. This is a consideration because steroid administration in the SLE flare state must be increased 2–3 times.<sup>3,4</sup> Side effects due to the use of INH are expected to worsen the condition of SLE patients; therefore, the administration of INH in SLE patients is still being considered.

There have been reports that INH may trigger SLE and such a condition is known as drug-induced lupus erythematosus (DILE); INH has also been reported to cause damage to the liver, known as drug-induced liver injury (DILI).<sup>14,17,18</sup> In most cases, the liver damage is mild and asymptomatic and is only detectable by measuring levels of liver enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). About 10–20% of patients taking INH have a transient increase in serum ALT levels that will return to normal without discontinuing the administration. However, several patients (less than 1–3%) experience severe liver damage and liver failure.<sup>14,19</sup> Increases in ALT and AST begin as early as 1 week and occasionally as late as 9 months after starting treatment with INH.<sup>14,19</sup>

Pharmacokinetic profile studies in monitoring INH levels to address the problems caused by ATD in other TB-vulnerable patient groups have been conducted. For example, a study in South Africa reported a decrease in half-life ( $t_{1/2}$ ) and area under the curve (AUC), and an increase in total clearance (Cl) in HIV TB patients compared to non-HIV TB.<sup>20</sup> Interestingly, pharmacokinetics and pharmacogenetics studies in HIV patients have shown that acetylation rate, gender, and CD4 count have influenced the pharmacokinetic profile of INH.<sup>21</sup> Another study has shown that the maximum INH concentration was lower in TB patients with DM than in TB patients without DM.<sup>22</sup>

Furthermore, changes in the pharmacokinetic profile of INH can be a factor in the onset of side effects. Hepatotoxicity or damage to the liver due to the use of INH (DILI) is often associated with the metabolic phase of the INH pharmacokinetic profile. Monitoring and examining the pharmacokinetic profile by measuring blood drug levels is one strategy to determine the fate of INH, in which the blood drug levels vary in each person, depending on how quickly the body absorbs and eliminates the drug.<sup>15,23</sup> Such monitoring is beneficial to assess inter- and intraindividual variability in INH pharmacokinetics, which may also explain the high response variability, such as poor drug exposure, high prevalence of drug-induced toxicity, and drug resistance.<sup>23,24</sup> However, there is no data on the pharmacokinetic characteristics of INH or other anti-tuberculosis drugs in SLE patients in Indonesia. Therefore, our study aims to explore the pharmacokinetic profile of INH in SLE patients.

## Methods

### Study Design and Population

An observational, cross-sectional study with a purposive sampling technique was designed, including adult females in remission with no TB infection who regularly visited the Rheumatology outpatients clinic at Dr. Hasan Sadikin Hospital

Bandung from January to August 2023. The sample size for this research was determined from earlier studies conducted in Tanzania involving adult TB patients, as well as studies focusing on TB in conjunction with diabetes mellitus, with a minimum requirement of 20 participants deemed adequate to characterize the pharmacokinetics of anti-TB medications.<sup>25,26</sup> Our study was conducted in accordance with the principles of the Declaration of Helsinki. All participants signed a written informed consent before being enrolled and oral isoniazid and vitamin B6 10 mg/day were then given for 10 days every morning on an empty stomach. The exclusion criteria were those who had INH allergy, liver or kidney disorders, and malignancy, as well as those who were pregnant or in a lactating period. In addition, examinations for anti-HIV, random blood sugar, ALT, and AST (an increase of  $\geq 2$  times the upper limit of normal),<sup>27</sup> creatinine levels ( $>1.5$  mg/dl),<sup>28</sup> and chest X-ray were performed to further exclude co-morbidities. Subjects who met the inclusion criteria were tested for ALT, and AST as a monitoring of the effect of isoniazid on the liver in SLE patients while taking the medication.<sup>28</sup> This study received ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran Bandung (No: 1113/UN6.KEP/EC/2022).

## Pharmacokinetics Study of Isoniazid

Oral isoniazid 300 mg/day (manufactured by PT Kimia Farma, Bandung, Indonesia, Batch No. I11506BJ) and vitamin B6 10 mg/day for 10 days were given to SLE patients every morning on an empty stomach. To ensure patient adherence to taking medication, patients are provided with a checklist of time to take medication and monitored every day by communication via text message. On day 10, the patients came in a fasting state and had not taken any medications since about 10 hours before blood collection. Blood was taken at hour 0 before taking INH and pyridoxine in front of the researcher. After taking the drug, the patients were then allowed to consume food.

The pharmacokinetic blood samples were further taken at 1, 2, 3, 4, and 8 hours after drug administration. Plasma was separated and stored at  $-80^{\circ}\text{C}$  until further INH measurement was conducted at the Pharmacokinetic Laboratory using a validated method by Ultra Performance Liquid Chromatography (UPLC; Waters, Serial G10CHA, Made in America). As described previously, the accuracy of the INH assay was between 99.6 and 109.0%, with intra- and inter-day coefficients of variation remaining below 7.9% across a measurement range of 0.15 to 15 mg/liter.<sup>29</sup>

The pharmacokinetic parameters were assessed using the add-in program PKSolver non-compartmental, a menu-driven add-in program in Visual Basic for Application (VBA). The terminal slope was automatically determined through regression analysis with the highest adjusted  $R^2$  value. The area under the curve (AUC) was calculated using the log-linear trapezoidal method, incorporating both the observed and extrapolated data. Drug concentrations beyond 8 hours up to 24 hours were estimated. The decline in drug concentration follows an exponential elimination profile, and the slope of the logarithmic drug concentration was calculated based on the last available data points. Using the calculated slope drug concentration 24 hours were predicted. Additional parameters were measured such as terminal half-life ( $t_{1/2}$ ), clearance (Cl/F), volume of distribution (V/F) based on the terminal slope ( $V_z$ ). The maximum plasma concentration ( $C_{\max}$ ) and the time to reach it ( $T_{\max}$ ) were derived from venous plasma data.

Acetylators status was determined phenotypically based on the isoniazid elimination half-life with a cut-off value of  $>2.2$  hours for slow acetylators and a cut-off value of  $\leq 2.2$  hours for non-slow acetylators.<sup>30</sup>

## Statistical Analysis

Patient characteristics and pharmacokinetic parameter data were presented descriptively. The Spearman's rho (rank correlation) test was used to determine the relationship between untransformed parameters of patient characteristics and pharmacokinetic parameters. Data were statistically analyzed using IBM SPSS v.21. The p values of  $<0.05$  were considered statistically significant.

## Result

### Characteristics of SLE Patients

Of the 23 patients screened, 2 females and 1 male did not meet the inclusion requirements, thus, a total of 20 female patients were included. Since our research site was a referral center for areas in West Java Indonesia, the majority of the

original ethnicity was Sundanese. The data regarding this had also been available in a previous study on the characteristics of SLE patients at Hasan Sadikin Hospital where the ratio of women and men was 22:1 and the majority of patients were Sundanese.<sup>6</sup> The average age of the subjects of this study was 35.5 years old (s.d. 9.43), and the length of SLE illness was 2.5 years (median, range 1–16 years), and all had a history or still taking methylprednisolone, calcium, and folic acid. From the results of SLEDAI observation, 17 patients had a score of 0 (remission) and 3 had a score of 1 to 4 both before and after INH, as shown in Table 1.

## Pharmacokinetic Analysis on INH

The pharmacokinetic analysis of INH 300 mg/day in SLE patients was shown in Table 2. There was interindividual variability in the pharmacokinetic parameters and a relatively consistent time to maximum concentration ( $T_{max}$ ).

**Table 1** Demographic and Laboratory Characteristics of Patients with Systemic Lupus Erythematosus in Dr. Hasan Sadikin Hospital, West Java Indonesia

| Characteristics             | n (%)    | Mean (SD) or Median (min - max)* |
|-----------------------------|----------|----------------------------------|
| Age (years)                 |          | 35.5 (9.43)                      |
| Weight (Kg)                 |          | 58.95 (15.55)                    |
| BMI (Kg/m <sup>2</sup> )    |          | 24.60 (5.59)                     |
| Length of illness (years)   |          | 2.5 (2.5)                        |
| Ethnicity                   |          |                                  |
| Sundanese                   | 17 (85)  |                                  |
| Javanese                    | 1 (5)    |                                  |
| Batak                       | 1 (5)    |                                  |
| Ambonese                    | 1 (5)    |                                  |
| Isoniazid dose (mg/kg)      |          | 5.5 (4.48–6.21)*                 |
| SLEDAI score pre treatment  |          |                                  |
| 0                           | 17 (85)  |                                  |
| 1 to 4                      | 3 (15)   |                                  |
| SLEDAI score post treatment |          |                                  |
| 0                           | 17 (85)  |                                  |
| 1 to 4                      | 3 (15)   |                                  |
| AST (U/L)                   |          |                                  |
| Pretreatment                |          | 18 (9.25)                        |
| Posttreatment               |          | 19.5 (11.75)                     |
| ALT (U/L)                   |          |                                  |
| Pretreatment                |          | 15.5 (7)                         |
| Posttreatment               |          | 16 (8)                           |
| Medication in use           |          |                                  |
| Methylprednisolone          | 20 (100) |                                  |
| Calcium                     | 20 (100) |                                  |
| Folic Acid                  | 20 (100) |                                  |
| Chloroquine                 | 17 (85)  |                                  |
| Azathioprine                | 15 (75)  |                                  |
| Mycophenolate mofetil       | 15 (75)  |                                  |
| Methotrexate                | 4 (20)   |                                  |
| Cyclosporine                | 3 (15)   |                                  |
| Cyclophosphamide            | 3 (15)   |                                  |
| Pulse steroid               | 3 (15)   |                                  |
| Aspilet                     | 3 (15)   |                                  |
| Amlodipine                  | 3 (15)   |                                  |
| Captopril                   | 6 (30)   |                                  |

**Note:** \*designated as median (min - max).

**Abbreviations:** BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine transaminase.

**Table 2** Pharmacokinetic of Isoniazid in Patients with Systemic Lupus Erythematosus in Dr. Hasan Sadikin Hospital, West Java Indonesia

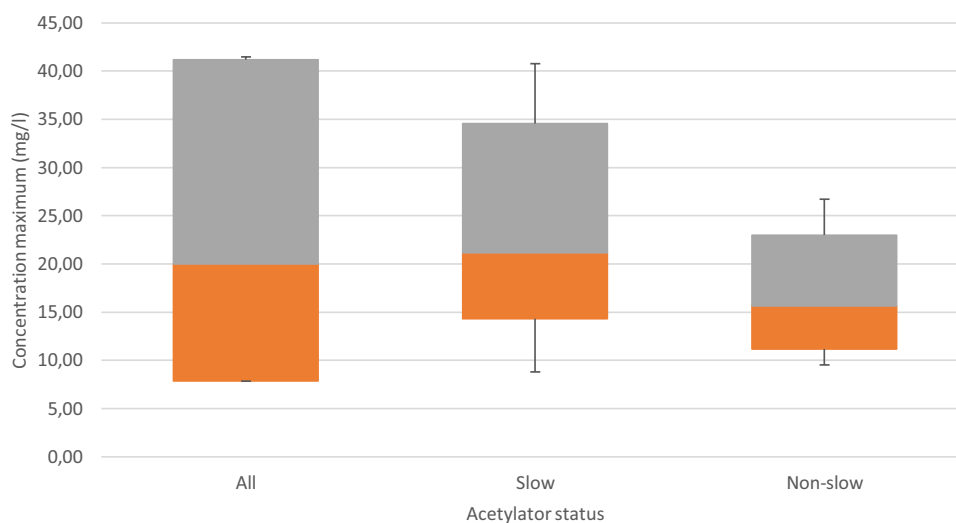
| Parameters                    | Total (n=20)        | Acetylator Phenotype <sup>#</sup> |                     |
|-------------------------------|---------------------|-----------------------------------|---------------------|
|                               |                     | Slow (n=7)                        | Non-slow (n=13)     |
| AUC <sub>0-24</sub> (mg.h/L)* | 28.01 (8.82–79.40)  | 57.85 (38.26–79.40)               | 18.95 (8.82–47.15)  |
| C <sub>max</sub> (mg/L)       | 8.63 (2.55–18.27)   | 10.73 (7.01–14.77)                | 7.67 (2.55–18.27)   |
| t <sub>max</sub> (h)          | 1 (1–2)             | 1 (1–2)                           | 1 (1–2)             |
| t <sub>1/2</sub> (h)          | 1.87 (0.91–3.61)    | 3.32 (3.13–3.61)                  | 1.37 (0.91–2.02)    |
| CL/F (L/h)                    | 10.82 (3.91–34.31)  | 5.25 (3.91–7.81)                  | 15.95 (6.50–34.31)  |
| V/F (L)                       | 29.18 (19.45–65.47) | 25.15 (19.83–36.39)               | 31.61 (18.96–65.47) |

**Notes:** <sup>#</sup>Acetylator status was determined by isoniazid elimination half-life >2.2 hours (slow acetylators) or ≤ 2.2 hours (non-slow). \*AUC<sub>0-24</sub> was significantly higher in slow acetylators compared to non-slow acetylators. Data t<sub>max</sub> in median (range), other data in Geomean (range).

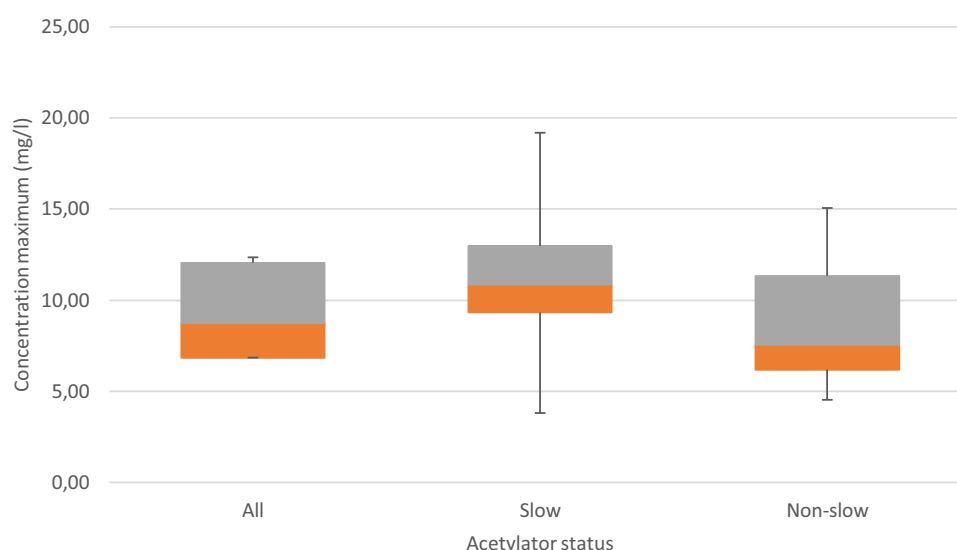
**Abbreviations:** AUC<sub>0-24</sub>, area under the time-concentration curve in plasma up to 24 h after the dose; C<sub>max</sub>, maximum plasma concentration; t<sub>max</sub>, time to C<sub>max</sub>; t<sub>1/2</sub>, half-life; CL/f, total clearance; V/f, apparent volume of distribution.

Geometric mean (GM) plasma AUC<sub>0-24</sub> and C<sub>max</sub> values of INH were 28.01 (8.82–79.40) mg.h/L and 8.73 (2.55–18.27) mg/L, respectively.

Furthermore, the SLE patients were categorized as slow (n=7) and non-slow acetylators (n=13) with a ratio of 1:1.86. The AUC<sub>0-24</sub> were significantly higher in slow acetylators compared to non-slow acetylators (57.85 vs 18.95 mg.h/L; p<0.01) as depicted in Figure 1; whereas no significant difference in C<sub>max</sub> (10.73 vs 7.67 mg/L; p>0.01) as shown in Figure 2. Interestingly, a strong correlation was observed between AUC<sub>0-24</sub> and C<sub>max</sub> (Spearman's rho=0.762, p<0.01). In addition, C<sub>max</sub> in plasma concentration showed no correlation with BMI and AST posttreatment (Spearman's rho = −0.45, p= >0.01 and 0.45, p= >0.01, respectively), neither with AUC<sub>0-24</sub> (Spearman's rho = −0.42, p= >0.01; 0.24, p = >0.01).



**Figure 1** The AUC<sub>0-24</sub> of isoniazid in patients with SLE from Indonesia (Log-transformed). Gray: 3<sup>rd</sup> quartile value of isoniazid; Orange: 2<sup>nd</sup> quartile value of isoniazid based on acetylator status.



**Figure 2** The  $C_{max}$  of isoniazid in patients with SLE from Indonesia (Log-transformed). Gray: 3<sup>rd</sup> quartile value of isoniazid; Orange: 2<sup>nd</sup> quartile value of isoniazid based on acetylator status.

## Discussion

SLE with TB complication is prevalent, especially in TB-endemic areas. The complex and reciprocal relationship between TB and SLE often worsens and may increase SLE morbidity and mortality. Isoniazid (INH) is the drug of choice recommended by WHO for preventive therapy in latent TB patients, especially in TB-prone groups such as HIV. However, due to the controversy of INH use in SLE groups, no specific guidelines recommending INH for TB preventive therapy in SLE groups. This study provides valuable insight into the pharmacokinetic profile of isoniazid in SLE patients in Indonesia.

SLE patients are at an increased risk of developing TB due to both the immunosuppressive nature of their disease and the medications they commonly use, such as corticosteroids and other immunosuppressants.<sup>10</sup> Several studies have indicated that SLE patients have an increased risk of developing drug-induced lupus (DIL) by INH since the use of INH potentially exacerbates the underlying autoimmune condition.<sup>14,16,17</sup> Determination of pharmacokinetic parameters through measurement of drug levels in the blood (serum or plasma) at a certain time describes the process of absorption, distribution, metabolism, and excretion in each individual which has an important meaning in reviewing the determination or provision of effective and safe doses for patients, especially in patients who must consume multiple drugs, diverse and in a long period of time such as in SLE patients.<sup>14,24</sup> The use of concomitant drugs in SLE patients may also have an effect as their interaction with INH may decrease the exposure to concomitant drugs or vice versa. To ascertain interactions between concomitant drugs and INH, searches were conducted through the websites <https://go.drugbank.com>, <https://reference.medscape.com>, and <https://www.pharmgkb.org>. Based on a review of available sources, several drug interactions with INH have been identified. Methylprednisolone reduces the effectiveness of INH through an unknown mechanism, while INH increases methylprednisolone levels by inhibiting CYP3A4 enzymes in the liver and gut, affecting its metabolism. Calcium carbonate decreases INH levels by inhibiting its gastrointestinal absorption, and isoniazid similarly reduces calcium carbonate levels through the same mechanism. This interaction applies only to the oral forms of both agents, and it is recommended that the administration of two drugs be spaced at least 2 hours apart. Additionally, folic acid may decrease the excretion rate of isoniazid, potentially leading to higher serum levels. However, despite 100% of SLE patients in this study receiving corticosteroids, calcium, and folic acid, the maximum plasma concentration of isoniazid remained at expected levels, suggesting that the observed drug-drug interaction may not have been significant in this study.<sup>31–33</sup>

INH given orally is easily absorbed. Absorption is impaired if INH is given with food. The bioavailability of orally administered INH is about 100% with the standard oral dose given being 300 mg or 5 mg/kg.<sup>14</sup> The drug diffuses into all

body fluids and cells. The level of INH in cerebrospinal fluid (CSF) is almost the same as that in serum or plasma. The ratio of INH in epithelial fluid to plasma is 1–2, and for CSF is 0.9.<sup>30</sup> In healthy people, peak plasma concentrations are reached between 3–5 mcg/mL within 1–2 hours,<sup>13</sup> that also similar in individuals with pulmonary TB or extrapulmonary TB, as well as in HIV individuals with TB.<sup>30,34</sup> Acetylator status emerged as a key predictor of INH plasma exposures in the univariable analysis, with slow acetylators exhibiting a threefold higher in AUC<sub>0–24</sub> compared to non-slow acetylators.

INH plasma exposures in SLE patients were comparable to those reported in previous studies involving patients with MDR-TB receiving high-dose INH with a similar distribution of slow and non-slow acetylators.<sup>35</sup> Thus, even though the absolute doses differ, the overall drug exposures in plasma may converge between these two groups due to the interplay of acetylator phenotypes and disease-related metabolic changes.

Understanding how INH is metabolized in this population is crucial, as pharmacokinetics can vary significantly due to genetic factors like variation in NAT2 acetylator status, which influences INH metabolism.<sup>11</sup> This study did not include genetic confirmation of acetylator status, however, existing literature indicates that genotypic assessments are consistent with phenotypic evaluations.<sup>30</sup>

When comparing the pharmacokinetics results in the SLE group with those from other groups, the median  $T_{max}$  and mean half-life ( $t_{1/2}$ ) in the SLE group in this study, were nearly identical to those observed in the TB group from a pharmacokinetic study conducted on TB patients in Indonesia.<sup>30</sup> Similarly, the median  $T_{max}$  in the SLE group and in healthy adults was reached within the first hour.<sup>23</sup> While the  $C_{max}$  and AUC<sub>0–24</sub> in this study were higher when compared to other groups like healthy persons, TB, HIV, and DM.<sup>20,22,30</sup> However, the results in this study were still in the therapeutic range. The  $C_{max}$  interval is generally estimated to occur between 1 and 2 hours to achieve a therapeutic effect while minimizing neurotoxic side effects.<sup>35</sup> Data from <https://go.drugbank.com> showed that plasma levels of isoniazid in slow inactivators treated with prednisolone were markedly lower compared to those who only received isoniazid and rifampin. In rapid inactivators, plasma concentrations of isoniazid were comparable in both patient groups, indicating that the simultaneous use of rifampin significantly altered the impact of prednisolone on the distribution of isoniazid in these individuals. In our study, all subjects were taking methylprednisolone and the resultant maximum concentration of isoniazid was still quite high, the drawback being that there is no comparative data on SLE patients without methylprednisolone.

In a systematic review of the efficacy, safety, and pharmacokinetics of isoniazid, the typical therapeutic range for the peak plasma concentration ( $C_{max}$ ) of INH is between 3 and 6 µg/mL.<sup>23</sup> The average  $C_{max}$  of INH in the adult slow acetylator (SA) groups ( $7.16 \pm 4.85$  µg/mL) did not significantly differ from that in the intermediate acetylator (IA) group ( $5.11 \pm 2.78$  µg/mL) ( $p > 0.05$ ) or the rapid acetylator (RA) group ( $4.84 \pm 3.60$  µg/mL) ( $p > 0.05$ ). Another pharmacokinetic parameter that reflects the effectiveness of INH is the area under the curve from 0 to 24 hours (AUC<sub>0–24</sub>). The average AUC<sub>0–24</sub> for INH was  $40.38 \pm 33.42$ ,  $15.48 \pm 4.68$ , and  $19.46 \pm 25.16$  µg h/mL in the SA, IA, and RA groups, respectively. The overall prevalence of drug-induced liver injury (DILI) was  $36.23 \pm 19.84\%$  in the SA group, which was significantly greater than that observed in the IA ( $19.49 \pm 18.20\%$ ) ( $p < 0.001$ ) and RA ( $20.47 \pm 20.68\%$ ) groups ( $p < 0.0001$ ). The prevalence of elevated liver enzyme levels showed a significant difference among the SA, IA, and RA groups ( $p = 0.042$ ). The average prevalence of elevated liver enzymes in the SA group was  $41.79 \pm 33.71\%$ , the highest among the different acetylator types. The onset time for DILI varied from 14 to 55.2 days, with a mean of  $26.07 \pm 15.46$  days.<sup>23</sup> In this study,  $C_{max}$  in (SA) (10.73 mg/L) and in non-slow acetylator (NSA) (7.67 mg/L) with (AUC 0–24) (SA) (57.85 mg.h/L) and (NSA) (18.95 mg.h/L), the only adverse event reported was nausea on the first day of INH consumption, which resolved the following day without the need to discontinue treatment, also without any increase in AST or ALT values (Table 2). This nausea may be related to INH intake, but several other factors could contribute to its occurrence, including the underlying condition of SLE, as gastrointestinal complaints are common in SLE patients.<sup>36</sup> Furthermore, the AST and ALT monitoring was only checked before INH and the last day of INH intake, and that limits our study, therefore, the clinical data for the efficacy of using INH as a long-term TB prophylaxis was not captured. Usually, patients will return to the hospital in the following month, and laboratory examinations are carried out to see the development of SLE disease and its complications, further actions of this study should collect data on subsequent visits.

Hepatotoxicity due to INH use generally occurs within weeks to months, rather than within days to weeks after the onset seen in hypersensitivity reactions.<sup>19,23</sup> Although our study has discussed INH-induced liver injury and drug-induced lupus, data on ALT/AST elevations over time is lacking. While no significant adverse effects were observed in this short-term study, future research should evaluate long-term INH hepatotoxicity and risk of drug-induced lupus in SLE patients. This metabolic change increases drug exposure even at lower doses. The results of this study are intended to guide the use of TB preventive therapy, especially INH administration in SLE patients in Indonesia. These findings may also help improve the effectiveness and safety of TB preventive efforts in the SLE group.

This study has limitations, including the small number of participants and the absence of male patients, therefore, the findings may not apply to male SLE patients due to potential differences in drug metabolism. Larger cohorts and inclusion of male patients are needed in the future. Moreover, *NAT2* genotyping to determine acetylator status has not been performed which may affect the pharmacokinetic profile of INH. However, the literature indicates that genotyping results are in line with phenotypic evaluation. Although phenotypic assessment cannot determine the genotype of the intermediate acetylator, this limitation may be seen as a drawback of the phenotypic approach to determining acetylator status. In contrast, phenotypic results may be viewed as more clinically relevant as they represent the actual manifestation of the genotype as demonstrated in our previous study in patients with TB meningitis.<sup>30</sup> Genotype validation in SLE patients in Indonesia warrants further study.

## Conclusion

SLE patients are at an increased risk of developing TB due to both the immunosuppressive nature of their disease and the medications they commonly use, such as corticosteroids and other immunosuppressants. Pharmacokinetically in SLE patients with an INH prophylaxis regimen of 300 mg/day showed achieved target  $C_{max}$  sufficient for TB prophylaxis without increasing side effects in SLE patients. This pharmacokinetic study is a preliminary study for further studies to understand more thoroughly the pharmacodynamic-related responses, drug-drug interactions, and pharmacogenetics of SLE patients treated with INH to ensure its efficacy and safety in the SLE population.

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## Author Contributions

All authors significantly contributed to the work presented, which includes aspects such as conception, study design, execution, data acquisition, analysis, and interpretation, or in all these areas; participated in drafting, revising, or critically reviewing the article; provided final approval for the version to be published; concurred on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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