CONTINUOUS USE OF ORAL CORTICOSTEROIDS AMONG AMBULATORY PATIENTS IN JEMBER DURING 2010-2011

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Abstract

Prolonged oral corticosteroid use was reported to be associated with several adverse effects, such as fractures and increased risk of developing tuberculosis (TB). This descriptive, prospective study was to observe the pattern of oral corticosteroid use and to find correlation between age, gender, and continuous use of oral corticosteroids in Jember, East Java, Indonesia. Continuous use was defined as receiving more than one oral corticosteroid prescription, and the duration between prescriptions was less than 3 months (90 days). Data were obtained from ambulatory claim database of *Asuransi Kesehatan* (Askes) of patients aged more than 18 years visiting dr. Soebandi Hospital, Jember from January 1, 2010 to October 31, 2011. Consecutively, 366 oral corticosteroid users were followed until October 31, 2011 starting from the time they received the first prescription. This study found that 14.9% (3,275/2,1907) Askes ambulatory patients accepted oral corticosteroid prescriptions. A number of 44.0% (160/366) patients were continuous users of oral corticosteroid with median (IQR) duration of use of 56 (20.5—133) days. Almost all patients (98.6%, 361/366) received dexamethasone 0.5 mg at a point of time. Multiple linear regression analysis showed positive, statistically significant (p=0.015) correlation between age, gender, interaction of both, and the logarithmic duration of continuous use of oral corticosteroid. Men were more likely to use oral corticosteroid than women after their 53th birthday. In conclusion, concern to prolonged use of oral corticosteroid should be more focused in older males than females in Jember.

Keywords: oral corticosteroid, pharmacoepidemiology, Jember, Indonesia, continuous use of medication, outpatient

I. INTRODUCTION

Corticosteroid drugs have been used for more than 75 years in modern medicine for several inflammatory-mediated diseases. The first synthetic corticosteroid, cortisol, was invented in 1939 by Edward Kendall and Tadeus Reichstein (Bouvard, Legrand, Audran, & Chappard, 2010; Marques, Silverman, & Sternberg, 2009). Following this invention two more corticosteroids, prednisolone and methylprednisolone, were first synthesized during 1950-1960 (Bouvard *et al.*, 2010). Pharmacodynamic properties of

corticosteroids as anti-inflammatory and immunosupresive agents on rheumatoid patients were first introduced in 1948 by Philip Hench and colleagues (Hunter & Blyth, 1999; Marques *et al*., 2009). These drugs have become the first line therapy for such conditions (Coutinho & Chapman, 2011).

Long-term use of corticosteroid drugs was however found to be associated with several deleterious effects. A large retrospective cohort study of 488,470 adult patients aged more than 18 years from the General Practice Research Database (GPRD) in the UK revealed that long-term use of oral corticosteroids was an independent risk factor of nonvertebral and vertebral fractures at relative rate of 1.33 (95% confidence interval, 1.29 –1.38) and 2.60 (2.31–2.92), respectively (van Staa, Leufkens, Abenhaim, Zhang, & Cooper, 2000). The association was also found to be dose-related in a positive manner. In 2004, a meta-analysis was published supporting this evidence (Kanis *et al.*, 2004). Despite increasing the risk of any fracture both in male or female populations, corticosteroid use was, more importantly, linked to increased risk of tuberculosis (TB) development. Deriving data from the UK's GPRD a well-designed case-control study with up to 4 controls matched to a new case of TB on 5 criteria found that the adjusted odds ratio of TB for current, recent, and past corticosteroid users were 4.9 (95% confidence interval, 2.9–8.3), 4.3 (1.6—11.1), and 1.4 (0.9—2.1), respectively, compared to nonusers (Jick, Lieberman, Rahman, & Choi, 2006). Inhaled corticosteroid, however, did not seem a risk factor of TB as recent research from Taiwan suggested (Lee *et al.*, 2013).

The association between corticosteroid use and increasing risk of TB then becomes an important knowledge in a population whose both factors are prevalent, Indonesia for instance. In 2013, the second highest incidence of acid-fast bacilli (AFB) smear-positive sputum test for TB in Indonesia was reported from East Java province, where the city of Jember is administratively located (Ministry of Health of Republic of Indonesia, 2014). To the extent of corticosteroid use, several studies show that this group of drug is tending to be used inappropriately in resource poor settings, such as in Iraq, Pakistan, and Kenya (Farooqi, Nasir-ud-Din, Aman, Qamar, & Aziz, 1997; Kamau & Oyoo, 2013; Mansour, Odaa, & Wanoose, 2010). This may suggest the prevalent use of corticosteroid in similar settings. To our knowledge, research on the use of corticosteroids remains limited in Indonesia. By conducting a hospital-based study, this

research aimed to describe the pattern of oral corticosteroid use, and to define the relationship between age, gender, and continuous use of oral corticosteroidsin Jember.

II. METHODS

A. Data Collection and Handling

Data of oral corticosteroid use during January 1, 2010 and October 31, 2011 in Jember were obtained from the ambulatory claim database of *Asuransi Kesehatan* (Askes), which has been renamed *Badan Penyelenggara Jaminan Sosial* (BPJS) since January 2014. Data were collected between November-December 2011 in pharmacy department of dr. Soebandi Hospital, Jember. Personal identification (member card number) and demographic information (name, date of birth, and gender) of patients were recorded into Microsoft Access database as well as the dispensing dates of prescription and the oral corticosteroid medications (International Nonproprietary Names, strength, and the dispensed number). The Askes database did not record the prescriber details, dosage regimen, and diagnosis.

Each patient aged 18 years or older was followed prospectively until October 31, 2011 after being identified receiving first oral corticosteroid treatment. If the first prescription was received 3 months (90 days) before October 31, 2011, the patients were not included in the study. Discontinuation of the treatment was applied for patients who did not refill or receive a new oral corticosteroid prescription during 3 months after their last prescription (van Staa, Leufkens, Abenhaim, Begaud, *et al.*, 2000). Sample size was calculated using StatCalc feature of Epi Info 7.1.5.2 software (Centers for Disease Control and Prevention (CDC), USA). For a population survey or descriptive study with expected frequency of 30%, the total sample needed was 323 subjects for 95% confidence interval. Consecutive sampling method was performed. Patients who received one prescription or more were included in the study. For modelling the outcome variable, however, those who only obtained one prescription were excluded.

Outcome variable was the duration of continuous oral corticosteroid treatment, whereas the predictors were gender and age. The age of patients was calculated based on the date of birth and the dispensing date of the first presciption. The duration of oral corticosteroid treatment was the days between the first and the last prescription. The treatment duration from the last prescription was not added into the calculation because

the data on dosage regimen cannot be obtained. Therefore, patients who received only one prescription cannot be considered to have had continuous treatment.

B. Statistical Analyses

All statistical analyses were performed using Stata 13.0 (StataCorp LP, USA). Descriptive analysis was to show the data distribution of patient's age and gender, the types of oral corticosteroid medications, the number of prescriptions received, and the duration of treatment. Multiple linear regression was used to model the duration of continuous oral corticosteroid treatment based on gender and age of patients (and their interaction, if exists). Recorded data in Microsoft Access database were exported into a Microsoft Excel format before being imported into Stata software. Data check was performed to ensure the completeness after format changes. Outcome variable was checked to comply with the normal distribution assumption. Transformation was conducted, if necessary, depending on the type of skewness. Regression diagnostic analyses were using residual, standardised residuals, and DFbeta to identify and control outliers and influential observations. The p-value of <0.05 was considered as statistically significant.

C. Permissions and Ethical Consideration

Permissions were asked to Lembaga Penelitian Universitas Jember, Bakesbanglinmas Office in Jember, and the dr. Soebandi Hospital before data collection. The names of patients were recorded to ease data handling. None except three researchers involved in this study knew the patient name. Data were stored in digital format in password protected computers. As patient's address was not recorded, the privacy was assumed to be safe.

III. RESULTS AND DISCUSSION

During the period from 1 January 2010 to 31 October 2011 a number of 21,907 ambulatory patients were recorded in the ambulatory Askes claim database of dr. Soebandi Hospital, Jember. Of them,14.9% (3,275/21,907) were oral corticosteroid users who received 8,174 ambulatory prescriptions. Literature on similar topic, setting, and timeframe is difficult to be accessed in full text. However, without accounting for setting and timeframe, the period prevalence of oral corticosteroid users resulted from this study was substantially lower than that point prevalence in urban Islamabad,

Pakistan (30.5%, 78/256), but markedly higher than the point prevalence across the UK (0.9%)(Farooqi *et al.*, 1997; van Staa, Leufkens, Abenhaim, Begaud, *et al.*, 2000).

Table 1 Sample Characteristics

Characteristics	**Value**
Total observations	366 patients
Age, mean ± SD	53.8 ± 12.9 years
Female, number (%)	212 (57.9)
Duration of oral corticosteroid treatment, median, IQR	0, 0-40 days
Duration of continuous oral corticosteroid treatment, median, IQR	56, 20.5-133 days
Logarithmic duration of continuous oral corticosteroid treatment, mean ± SD	3.9 ± 1.2
Oral corticosteroid prescriptions, number of patients (%)	
1 prescription	206 (56.3)
2 prescriptions	71 (19.4)
3 prescriptions	38 (10.4)
4 prescriptions	16 (4.4)
5 prescriptions	8 (2.2)
6 prescriptions	10 (2.7)
7 prescriptions	5 (1.4)
8 prescriptions	5 (1.4)
9-19 prescriptions	5 (1.4)
≥ 20 prescriptions	2 (0.4)
Oral corticosteroids, number of patients (%)*	
Dexamethasone 0.5 mg	361 (98.6)
Methylprednisolone 4 mg	163 (44.5)
Methylprednisolone 8 mg	3 (0.8)
Prednisone 5 mg	67 (18.3)

SD: standard deviation; IQR: inter-quartile range; *The sum was not 100% as a patient may use more than one medications.

A number of 366 patients were followed up from their first oral corticosteroid prescription to the last one (Table 1). The duration of continuous treatment was positively skewed. Hence, logarithmic transformation was performed, yielding a better distribution. More than half of patients (206/366, 56.0%) were only received one prescription, leaving the remainder 44.0% (160/366) for multivariable analysis. More detailed, none of patients received 9 consecutive prescriptions and only two patients obtained ≥20 continuous prescriptions in this study. If the findings by Jick and colleagues (2006) is applicable to this study, 56.0%, 42.2%, 1.4%, and 0.4% of ambulatory patients in Jember had at least 3.2, 7.0, 8.7, and 4.1 increasing risk of developing pulmonary TB than nonuser of oral corticosteroids. The risk could be higher

as the city was known to be prevalent in new TB cases. Almost all patients in the present study (361/366, 98.6%) were dexamethasone 0.5 mg users. Similar corticosteroid medication was used amongst nonprescription users of corticosteroids (438/682, 64.2%) in Basrah, Iraq (Mansour *et al.*, 2010).

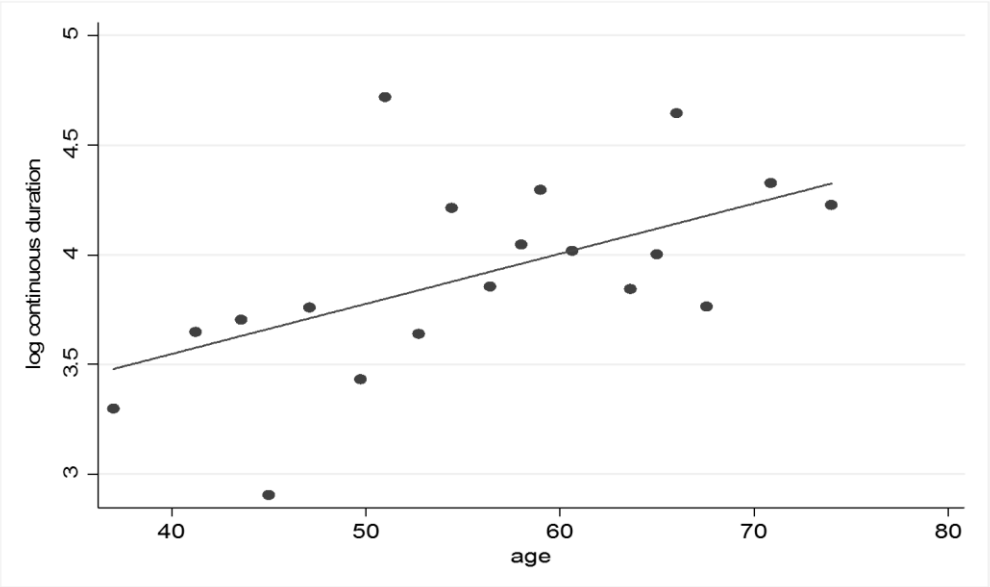

Figure 1 Scatter-plot of age vs logarithmic continuous duration of corticosteroid use

Without taking account gender into the regression analysis, the positive correlation was found between age and logarithmic duration of continuous treatment (Figure 1). However, interaction between age and gender occurred and affected the regression model (Figure 2). Positive correlation between age and logarithmic duration of continuous treatment persisted for both gender, even though the slope of regression line for males was steeper than for females. Before reaching approximately the age of 53 years, the continuous oral corticosteroid treatment in males was shorter in duration compared to females. However, the trend was inverse afterwards. The final model equation was as follow:

$$\hat{y} = 1.59 + 1.85\ (a) +\ 0.04\ (b) - 0.03\ (a \times b)$$

Where

y : log duration of continuous oral corticosteroid use

a : patient's gender (1 if female and 0 if male)

b : patient's age, in years

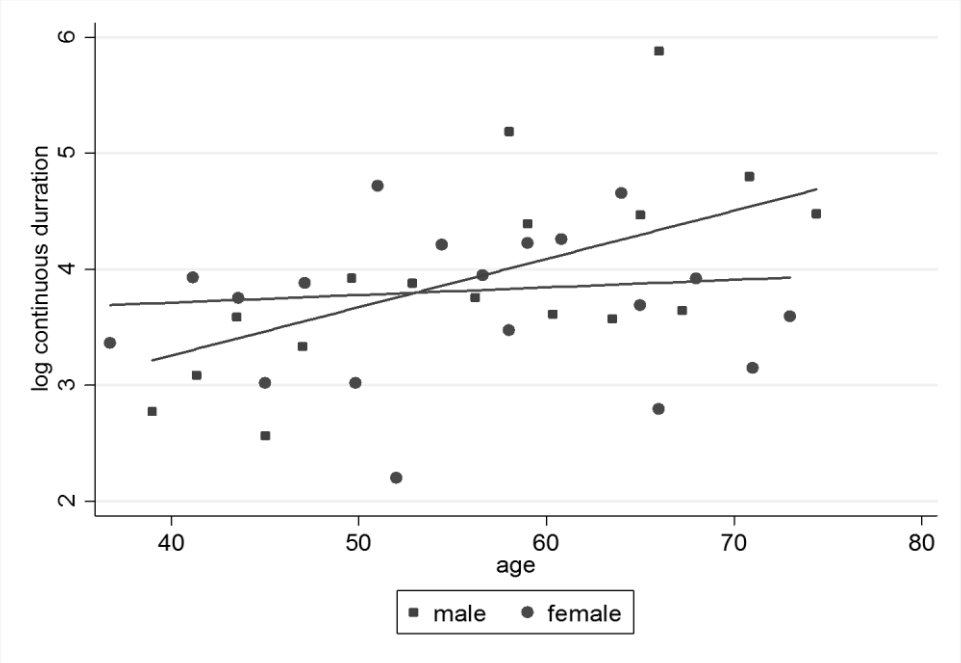

Figure 2 Interaction between age and gender

The minimum and maximum age were 32 and 79 years, respectively. Only 142 observations were involved into the linear regression modelling. The remainder 18 observations were excluded as DFbeta analysis results showed them as influential cases.

Although this study presented statistically significant model (p=0.015), the equation seemed inapplicable because only three explanatory variables were included in the multivariable analyses. As supported by the adjusted R^2 of 5.32%, only small variations in the duration of continuous use of oral corticosteroid were explained by age, gender, and interaction of both. Of course, above all, patient's conditions, doctor's diagnosis and prescribing habit, may contribute more to the equation. Such factors were not recorded in our data source and became the limitation of the present study. The other limitation was that the first prescription was not the real "first prescription" the patient ever received as the data were not taken comprehensively. Despite those limitations, this study to authors' knowledge was one of pioneers of research employing electronic health claim database in the country.

IV. CONCLUSION

In conclusion, concern to long-term oral corticosteroids use in Jember should be focused more on older male patients undergoing ambulatory care than female patients.

Education for self-recognition of adverse effects of corticosteroids should be considered in the routine ambulatory pharmacy service in the near future.

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REFERENCE

Bouvard, B., Legrand, E., Audran, M., & Chappard, D. 2010. Glucocorticoid-induced Osteoporosis: a Review. Clinic Rev Bone Miner Metab, 8: 15–26

Coutinho, A. E., & Chapman, K. E. 2011. The Anti-Inflammatory and Immunosuppressive Effects of Glucocorticoids, Recent Developments and Mechanistic Insights. Mol Cell Endocrinol, 335(1): 2–13

Farooqi, A. Z., Nasir-ud-Din, Aman, R., Qamar, T., & Aziz, S. 1997. Corticosteroid Use and Abuse by Medical Practitioners for Arthritis and Related Disorders In Pakistan. Br J Rheumatol, 36(1): 91–4

Hunter, J. A., & Blyth, T. H. 1999. A Risk-Benefit Assessment of Intra-Articular Corticosteroids in Rheumatic Disorders. Drug Saf, 21(5): 353–365

Jick, S. S., Lieberman, E. S., Rahman, M. U., & Choi, H. K. 2006. Glucocorticoid Use, Other Associated Factors, and The Risk of Tuberculosis. Arthritis Rheum, 55(1): 19–26

Kamau, E., & Oyoo, G. 2013. Steriod Abuse; Two Wrongs Don't Make A Right: A Case Report. Afr J Rheumatol, 1(2): 28–30

Kanis, J. A., Johansson, H., Oden, A., Johnell, O., Laet, C. De, Iii, L. J. M., … Mellstrom, D. 2004. A Meta-Analysis of Prior Corticosteroid Use and Fracture Risk. J Bone Miner Res, 19(6): 893–899

Lee, C.-H., Lee, M.-C., Shu, C.-C., Lim, C.-S., Wang, J.-Y., Lee, L.-N., & Chao, K.-M. 2013. Risk Factors for Pulmonary Tuberculosis in Patients with Chronic Obstructive Airway Disease in Taiwan: A Nationwide Cohort Study. BMC Infect Dis, 13(1): 194

Mansour, A., Odaa, A., & Wanoose, H. 2010. Corticosteroid Nonprescription Use: A Cross-Sectional Hospital-Based Study in Basrah. Med Princ Pract, 19: 182–187

Marques, A. H., Silverman, M. N., & Sternberg, E. M. 2009. Glucocorticoid Dysregulations and Their Clinical Correlates. Ann N Y Acad Sci, 1179: 1–18

Ministry of Health of Republic of Indonesia. 2014. [Indonesia Health Profile 2013].

van Staa, T. P., Leufkens, H. G. M., Abenhaim, L., Begaud, B., Zhang, B., & Cooper, C. 2000. Use of Oral Corticosteroids in the United Kingdom. Q J Med, 93: 105–111

van Staa, T. P., Leufkens, H. G. M., Abenhaim, L., Zhang, B., & Cooper, C. 2000). Use of Oral Corticosteroids and Risk of Fractures. J Bone Miner Res, 15(6): 993–1000.