

Effect of the Compulsory Licensing Policy on the Access to Selected Medicine in Thailand

ผลต่อการเข้าถึงยาของนโยบายบังคับใช้สิทธิเหนือสิทธิบัตรยาในประเทศไทย

Suthira Taychakhoonavudh (สุธีรา เตชคุณวุฒิ)* Dr.Paitoon Kraipornsak (ดร.ไพฑูรย์ ไกรพรศักดิ์)**

Dr.Sauwakon Ratawijitrasin (ดร.เสาวคนธ์ รัตนวิจิตรศิลป์)***

ABSTRACT

The aim of this study was to have a first field evaluation of the effect of compulsory licensing policy implementation on the access to the announced medicine. This study was a descriptive retrospective study using electronic medical and pharmaceutical prescription data from 3 hospitals in 3 levels of health care settings; university hospital, regional hospital and general hospital from the period of 2007 to 2009. Time series analysis was employed to analyze the relationship between the numbers of patients receiving each announced medicine and the effect of the compulsory licensing policy implementation. Following the implementation of compulsory licensing policy, the number of patients receiving Clopidogrel has significantly increased by 55.68%. While the number of patients receiving Lopinavir/ritonavir has also significantly increased by 26.78%, number of patients receiving Efavirenz has significantly decreased by 25.86%. However, as a whole, access to antiviral drug has been increased. This result may be directly related to the policy and indicates that this method is successful in increasing the access to only some particular category of drugs. Quality of the compulsory licensed medicine should also be further studied since it is one of the most concerning factor by the physician who prescribe the medicine.

บทคัดย่อ

การวิจัยครั้งนี้มีวัตถุประสงค์เพื่อประเมินผลของการบังคับใช้สิทธิเหนือสิทธิบัตรยาต่อการเข้าถึงยาที่มีการบังคับใช้สิทธิบัตรยาได้แก่ Clopidogrel, Efavirenz และ Lopinavir/ritonavir ในโรงพยาบาล 3 แห่ง การศึกษาวิจัยนี้เป็นการศึกษาข้อมูลย้อนหลัง (Retrospective) โดยใช้ข้อมูลจากฐานข้อมูลอิเล็กทรอนิกส์ของโรงพยาบาลมหาวิทยาลัย 1 แห่ง, โรงพยาบาลศูนย์ 1 แห่ง และโรงพยาบาลทั่วไป 1 แห่ง ระหว่างปี 2550 ถึง ปี 2552 และนำมาวิเคราะห์แบบจำลองอนุกรมเวลาเพื่อทดสอบระดับนัยสำคัญของตัวแปรหุ่นของการมียา Generic ที่มีการบังคับใช้สิทธิบัตรในโรงพยาบาลแต่ละแห่งที่ส่งผลต่อจำนวนผู้ป่วยที่ได้รับยาที่มีการบังคับใช้สิทธิบัตรทั้ง 3 ชนิด จากผลการศึกษาพบว่าหลังจากการมียา Generic ที่มีการบังคับใช้สิทธิบัตรในโรงพยาบาลแต่ละแห่ง จำนวนผู้ป่วยที่ได้รับยา Clopidogrel เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ เช่นเดียวกับจำนวนผู้ป่วยที่ได้รับยา Lopinavir/ritonavir แต่จำนวนผู้ป่วยที่ได้รับยา Efavirenz กลับมีจำนวนลดลงอย่างมีนัยสำคัญทางสถิติ อย่างไรก็ตามโดยรวมแล้วผู้ป่วย HIV สามารถเข้าถึงยาด้านไวรัสได้มากขึ้นหลังจากมียา Generic ที่มีการบังคับใช้สิทธิเหนือสิทธิบัตรยาถึงแม้การบังคับใช้สิทธิเหนือสิทธิบัตรยาของกระทรวงสาธารณสุขจะสามารถเพิ่มการเข้าถึงยาบางชนิดได้มากขึ้น ปัจจัยด้านคุณภาพของยาควรจะได้รับการศึกษเพิ่มเติมเนื่องจากเป็นปัจจัยที่แพทย์ผู้สั่งจ่ายยายังคงกังวลต่อยา Generic ที่นำมาใช้หลังจากการบังคับใช้สิทธิเหนือสิทธิบัตร

คำสำคัญ : นโยบายบังคับใช้สิทธิเหนือสิทธิบัตรยา การเข้าถึงยา

Key Words : Compulsory licensing, Access to medicine

* Master degree student, Health Economics, Faculty of Economics, Chulalongkorn University

** Associate Professor Dr. Paitoon Kraipornsak, Faculty of Economics, Chulalongkorn university

*** Associate Professor Dr. Sauwakon Ratawijitrasin, Faculty of Social Sciences and Humanities, Mahidol university

Introduction

Compulsory Licensing, an action that complies with the flexibilities of the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS) allows the government to authorize itself or third parties the right to use the patents without authorization from the patent holder for the reason of the public policy (World Trade Organization, 1994).

Access to essential medicine is one of the major public health problems. Approximately thirty percent of the world's population, over 1.7 billion people, has inadequate access or no access at all to essential medicines (World Health Organization, 2004). Several countries, for example USA, Canada, India, Zimbabwe, Malaysia, Zambia and Indonesia (Sripen *et al*, 2008), have used compulsory licensing as a tool to relieve the problem of medicine inaccessibility. However, compulsory licensing is still a controversial issue in balancing between the human rights in access to essential medicine and promoting the innovation by giving incentives to inventors.

Thailand, like other countries in the world is also facing the access to medicine problems especially in HIV/AIDS patients. A study of Thai Working Group on HIV/AIDS Projection (2001) has showed that cumulative number of HIV infected patients in 2007 was an estimated 1,109,000 comprised of 508,300 patients that required continuing care and treatment. Even the number of new HIV cases is decreasing in recent years; these HIV patients need the patented second-line treatment medicine.

According to Thai Government, after several negotiations (Compulsory Licensing Information Center, 2008a) with the pharmaceutical company in order to reduce the price of the patented medicine, finally in late

2006 and early 2007, Thai Government announced its intention to introduce the government use of patents for 3 pharmaceutical products, including 2 antiretrovirals (ARVs): efavirenz (Ministry of Public Health, 2006) and lopinavir/ritonavir combination (Ministry of Public Health, 2007a). And drug for heart disease: clopidogrel (Ministry of Public Health, 2007b). According to the Ministry of Public Health (MOPH), the implementation of this policy aims at ensuring access to affordable medicines in the public sector. The action complied with the flexibilities of the TRIPs Agreement and the Thai patent Act (Thai Patent Act, 1979).

The aim of this study was to have a first field evaluation of the effect of compulsory licensing policy implementation on the access to the announced medicine comparing them to prior level of access at 3 hospitals, Thailand. Access to medicine in the analysis is comparing by using the number of patients receiving each medicine. Level of Hospitals was also added in the model in order to determine the effect of the level of health care settings on the accessibility before and after the implementation of compulsory licensing policy.

Materials and methods

Design and Data Sources

Descriptive retrospective study was conducted aimed at evaluating the change of access of the announced medicine. Access to the announced medicine in this study employed definitions of the access to medicine developed by MSH and WHO. (Management Science for Health and World Health Organization, 2000).

Secondary data which is electronic medical and pharmaceutical prescription data from 3 hospitals in 3 levels of health care settings; university hospital, regional

hospital and general hospital from the period of 2007 to 2009 were retrieved weekly from Pharmaceutical System Research and Intelligence Center's (PSyRic) prescription database to evaluate the change on the access to medicine after compulsory licensing.

Data Analysis

Number of patients receiving each announced medicine (Efavirenz, Lopinavir/ritonavir combination and Clopidogrel) in each week will be extracted from the database. Patients receiving CL announced medicine were defined as patients who received at least one prescription of Efavirenz or Lopinavir/ritonavir or Clopidogrel between 2007 and 2009. Time series analysis was employed to analyze the relationship between the number of patients receiving each announced medicine (dependent variables) and time trend, the effect of the compulsory licensing policy, and the level of hospital (independent variables). The following linear regression models were specified to compare the numbers of patients receiving each announced medicine before compulsory licensing and following the compulsory licensing in each hospital using dummy variable added in the model. The effect of the hospital on the number of patients receiving each announced medicine will be shown in the coefficient of another dummy variable.

Clopidogrel;

$$\text{Log}(\text{nu_pts}) = \beta_0 + \beta_1 \text{Log}(t) + \beta_2 \text{Dimple} + \beta_3 \text{hosplevel} + e_t$$

Efavirenz and Lopinavir/ritonavir;

$$\text{Log}(\text{nu_pts}) = \beta_0 + \beta_1 \text{Log}(t) + \beta_2 \text{Dimple} + \beta_3 \text{hosplevel1} + \beta_4 \text{hosplevel2} + e_t$$

Data were analyzed with the use of Eview software, version 5.1.

Results and discussion

Results

Table 1 shows the availability of the CL medicine in each hospital before and after the CL policy has been implemented. Compulsory licensed clopidogrel is still not available in the selected university hospital owing to the hospital policy toward the CL medicine. On the contrary, after the Compulsory licensed clopidogrel was available in regional hospital, the original version of clopidogrel has been withdrawn from the hospital drug list which similar to general hospital.

Efavirenz and Lopinavir/ritonavir both original and compulsory licensed were available in the university hospital prior and after the implementation of compulsory licensing policy. However, in the regional and general hospital, original Efavirenz and Lopinavir/ritonavir were available before the implementation of CL policy and only compulsory licensed medicine are available once the policy has been implemented.

Table 1 Availability of the CL medicine in each hospital before and after the CL policy has been implemented

Medicine	Type of Medicine	University Hospital		Regional Hospital		General Hospital	
		Before CL	After CL	Before CL	After CL	Before CL	After CL
Clopidogrel	Original	Yes	Yes	Yes	N/A	Yes	N/A
	CL	N/A	N/A	N/A	Yes	N/A	Yes
Efavirenz 200 mg	Original	Yes	Yes	Yes	N/A	N/A	N/A
	CL	N/A	Yes	N/A	Yes	N/A	N/A
Efavirenz 600 mg	Original	Yes	Yes	Yes	N/A	Yes	N/A
	CL	N/A	Yes	N/A	Yes	N/A	Yes
Lopinavir/ritonavir	Original	Yes	Yes	Yes	N/A	Yes	N/A
	CL	N/A	Yes	N/A	Yes	N/A	Yes

Table 2 Descriptive Statistics of the variables in Clopidogrel Dataset N=266

variable	description	mean	se
ln nu_pts	Natural log of number of patients receiving clopidogrel	2.534131	1.112195
ln t	Natural log of time (week)	3.915648	0.938455
dimple	Dummy variable for the implementation of CL policy (0=before CL; 1=thereafter)	0.293233	0.456103
hosplevel	Dummy variable for Hosplevel (0=general hospital, 1=regional hospital)	0.5	0.500943

Table 3 Descriptive Statistics of the variables in Lopinavir/ritonavir Dataset N=313

variable	description	mean	se
ln nu_pts	Natural log of number of patients receiving lopinavir/ritonavir	1.870028	0.963023
ln t	Natural log of time (week)	3.793607	0.893945
dimple	Dummy variable for the implementation of CL policy (0=before CL; 1=thereafter)	0.650655	0.477808
hosplevel1	Dummy variable for Hosplevel1 (1=university hospital, 0=else)	0.449782	0.498561
hosplevel2	Dummy variable for Hosplevel2 (1=regional hospital, 0=else)	0.423581	0.495208

Table 4 Descriptive Statistics of the variables in Efavirenz Dataset N=392

variable	description	mean	se
ln nu_pts	Natural log of number of patients receiving Efavirenz	3.14496	1.360977
ln t	Natural log of time (week)	3.952184	0.891334
dimple	Dummy variable for the implementation of CL policy (0=before CL; 1=thereafter)	0.815934	0.388071
hosplevel1	Dummy variable for Hosplevel1 (1=university hospital, 0=else)	0.357143	0.479817
hosplevel2	Dummy variable for Hosplevel2 (1=regional hospital, 0=else)	0.35989	0.480629

Table 2, 3 and 4 show the variable names, description, mean, and standard error of each dataset: Clopidogrel, lopinavir/ritonavir, and Efavirenz, respectively.

The results of the best-fit regression model of Clopidogrel, lopinavir/ritonavir, and Efavirenz is shown in Table 5, 6, and 7. The adjusted R square of the Clopidogrel, Lopinavir/ritonavir and Efavirenz regression are 0.56, 0.64 and 0.88, with an F statistic of 103.98, 101.38 and 327.82 and a probability-value of F statistics <0.0001 respectively indicating that the model explains a large part of the variation of number of patients receiving each medicine.

Table 5 Fitted explanatory model of number of patients receiving Clopidogrel

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	0.1347	0.2523	0.5338	0.5940
LOG(T)	0.3600	0.0642	5.6064	0.0000
DIMPLE	0.5568	0.1221	4.5613	0.0000
HOSPLEVEL	1.4438	0.0953	15.1529	0.0000

Adjusted R-squared = 0.56
F Statistic = 103.98 Prob(F-statistic) < 0.00001

Table 6 Fitted explanatory model of number of patients receiving Lopinavir/ritonavir

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-1.943275	0.254257	-7.642954	0.0000
LOG(T)	0.478159	0.070123	6.81887	0.0000
DIMPLE	0.267824	0.12973	2.064472	0.0401
HOSPLEVEL1	2.289027	0.126525	18.09153	0.0000
HOSPLEVEL2	1.878114	0.126417	14.85655	0.0000

Adjusted R-squared = 0.64
F Statistic = 101.38 Prob(F-statistic) < 0.00001

Table 7 Fitted explanatory model of number of patients receiving Efavirenz

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	0.4746	0.1353	3.5086	0.0005
LOG(T)	0.2212	0.0468	4.7315	0.0000
DIMPLE	-0.2586	0.1089	-2.3756	0.0180
HOSPLEVEL1	2.5688	0.0638	40.2818	0.0000
HOSPLEVEL2	3.0276	0.0625	48.4559	0.0000

Adjusted R-squared = 0.88
F Statistic = 327.82 Prob(F-statistic) < 0.00001

The constant term (c) in each equation estimated the baseline level of the number of patients receiving each medicine in general hospital at time zero.

36.00%, 47.81%, and 22.12% of Number of patients receiving Clopidogrel, Lopinavir/ritonavir, and Efavirenz were significantly ($p < 0.00001$) increased when the time change. After the implementation of compulsory licensing policy, number of patients receiving Clopidogrel has been increased by 55.68% ($p < 0.00001$) and number of patients receiving Lopinavir/ritonavir has been increased by 26.78% ($p = 0.0401$) respectively. In contrast, the number of patients receiving Efavirenz has been decreased by 25.86% ($p = 0.0180$) after compulsory licensing policy has been implemented.

Level of hospital has show a large effect on the number of patients receiving each medicine. Numbers of patients receiving Clopidogrel and Lopinavir/ritonavir are higher in regional hospital comparing to general hospital by 144.38% and 187.81% respectively. Similarly, number of patients receiving Lopinavir/ritonavir is 228.90% higher in university hospital than general hospital.

The effect of hospital level has shown the same result in number of patients receiving Efavirenz which is

302.76% higher in regional hospital comparing to general hospital. However, it has produced a different result in university hospital. Number of patients receiving Efavirenz is only 256.88% higher than general hospital which is less than regional hospital.

Discussion

According to the Ministry of Public Health, Compulsory licensing policy has been implemented in order to alleviate the access to medicine problems. In this study, it was showed that a change from prior-compulsory licensing policy to after-compulsory licensing policy was associated with a substantial increase in number of patients receiving Clopidogrel and Lopinavir/ritonavir. However, this effect has not been shown in the number of patients receiving Efavirenz. This result may be directly related to the policy and indicates that this method is successful in increasing the access to only some particular category of drugs. It has been shown that the change in the prescription of Clopidogrel and Lopinavir/ritonavir are more sensitive to the change of price than Efavirenz. Policy makers should also take this factor into an account when come to a decision in which medicine should be chosen to compulsory licensed.

Level of hospital should also be considered as one of the major factor. Access to some medicine may not be an issue in some level of hospital comparing to other level of hospital. Number of patients receiving some medicine may be higher in lower level of hospital due to patients' characteristic, complication of patient's disease and prevalence of disease. It should also be noted that even the number of patients receiving Clopidogrel may increase significantly; university hospital where

compulsory licensed Clopidogrel is not available has not been included in the analysis.

Some limitations in this study should be noted. Since quality of medicine and/or patient's clinical outcome has not been included in this time series analysis. It was assumed that the quality of original and compulsory licensed medicine is equal and would produce the same outcome. Study (Soumerai *et al*, 1991) found that health system components are interrelated and it is possible that the policy implementation affected other areas. The study of effectiveness of compulsory licensed medicine should also be done in order to assure the quality of these medicines. Given that the study is the first field evaluation, further study on the effect of compulsory licensing policy on the access to these medicines in more hospitals should also be done. The effect of the compulsory licensing policy on patient's outcome should be further studied as an indicator to policy success.

Conclusions

The introduction of a compulsory licensing policy to increase access to medicine was associated with the increase in number of patients receiving Clopidogrel and Lopinavir/ritonavir. However, the number of patients receiving Efavirenz has been decreased after the implementation of compulsory licensing policy. Accordingly, the overall access to antiviral drug has been increased. Level of hospital also has an impact on the access to medicine. Number of patients receiving medicine is higher in university hospital, regional hospital and general hospital respectively. However, this doesn't apply to every category of medicine.

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