An-Najah National University

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In vitro and *in vivo* Post-marketing Surveillance of Rosuvastatin among Palestinian Patients

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Dedication

To my father Yusuf,,

To my mother Afaf,,

To my sister and brothers Baylasan, Asem and Abdullah,,

Acknowledgement

I would like to express my gratitude and appreciation to Prof. Abdel Naser Zaid and Dr. Rowa' Al Ramahi for their guidance and encouragement throughout this research project. I also wish to thank Dr. Mohamad Alkhraz for his support during this project. I would also like to thank the team in Pharmacare company for their guidance in this project. Finally, I am so grateful to my family and friends for all the unconditional help.

الاقرار

أنا الموقعة أدناه، مقدّمة الرسالة التي تحمل العنوان:

***In vitro* and *in vivo* post-marketing surveillance of Rosuvastatin among Palestinian patients**

أقر بأن ما اشتملت عليه هذه الأطروحة إنما هو نتاج جهدي الخاص، باستثناء ما تمت الاشارة إليه حيثما ورد. وأن هذه الرسالة كاملة، أو اي جزء منها لم يقدم من قبل لنيل اي درجة او لقب علمي او بحثي لدى أي مؤسسة تعليمية أو بحثية أخرى.

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: اسم الطالبة: نورس يوسف عبد الله رضواني

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Date: التاريخ: 4.1.2021

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List of Abbreviations and Unites

API	Active pharmaceutical ingredient
ADR	Adverse drug reactions
AUC	Area under the curve
dL	Deciliter
FDA	Food and Drug Administration
HDL	High density lipoprotein
HPLC	High performance liquid chromatography
IRB	Institutional Review Board
JD	Jordanian Dinar
L	Liter
LDL	Low density lipoprotein
C max	Maximum plasma concentration
µl	Microliter
µm	Micrometer
Mg	Milligrams
Ml	Milliliter
Mmole	Millimoles
MOH	Ministry of Health
M	Molar
nm	Nanometer
N	Newton
RV	Rosuvastatin
Rpm	Round per minute
Std. deviation	Standard deviation
TG	Triglycerides
UV	Ultraviolet
USP	United States Pharmacopeia
WHO	World Health Organization

In vitro and *in vivo* post-marketing surveillance of Rosuvastatin among Palestinian patients

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Abstract

Background:

Hypercholesterolemia is a disease characterized by high cholesterol levels in the blood circulation due to elevated lipid biosynthesis in the liver or over consumption of foods with relatively high cholesterol content, mainly of animal sources. Rosuvastatin (RV) was approved for medical use in 2003, it is considered one of the most potent statins, it is used to reduce plasma cholesterol levels (hypercholesterolemia) and for the prevention of cardiovascular diseases in combination with exercise, diet, and weight-loss. RV is available in only two strengths in Palestine, 10 mg and 20 mg. The objectives of this study are to evaluate the quality of different pharmaceutical products containing RV which are available in the Palestinian market and to assess the safety and efficacy.

Method:

The methodology of this research study can be divided into two stages. In the first stage *in vitro* post-marketing quality control of the available RV tablet products was assessed through testing their general quality including visual quality such as color, shape , and presence of any

coating defects. In addition, the pharmacopeial quality such as weight uniformity, hardness, friability, and disintegration time were tested . High-performance liquid chromatography (HPLC) was used to assess the assay and dissolution profiles of the tested tablet products. The second stage was an *in vivo* post-marketing surveillance to assess the safety and effectiveness of RV medications.

Results:

Four different brand and generic of RV tablet products were available in the Palestinian pharmaceutical market (F1, F2, F3, F4) in both strength 10 and 20 mg/tablet. Initially, they were subjected to visual inspection. They showed good visual quality and there were no signs of abnormalities in the shape, color, or any sign of film coat defects. All products showed weight uniformity. Moreover, the disintegration time of all RV tablet products was within the range of 2-3 minutes. The assay of RV was within the accepted pharmacopeial levels in all tested tablets**.** The percentage of the drug content in the formulations F1, F2, F3 and F4 of 10 mg strength was 108.3%, 106.4%, 107.5% and 98.38% respectively. Moreover, for 20 mg strength the drug content was 109.2%, 103.4%, 107.77% and 104.2% for the RV formulations F1, F2, F3, and F4 respectively.

All the tested RV products showed a full release of the active ingredient RV within 30 minutes in the dissolution media at pH 6.6. Regarding RV products containing 10 mg of the API, the percentage of the drug release

for F1, F2, F3, and F4 were 105.3%, 86.37%, 97.28% and 108.96 respectively. Regarding RV tablet products containing 20 mg of the drug, the percentage of released RV was 96.32%, 101.74%, 98.99% and 89.62% for the formulations F1, F2, F3 and F4 respectively.

Concerning *in vivo* surveillance study, ninety-four cases were collected from the internal clinic at An-Najah hospital in Nablus. Respondents were mainly females (55.3%). The age distribution was between 27 - 83 years. The majority of the participants were using other medications in addition to RV (81.9%). Furthermore, RV treatment showed that 37.2% of patients were prescribed the dose of 10 mg. The most frequent adverse effect was muscle pain (51.1%). The next side effect was headache with a percentage of 26.6%, while 24.5 % of the included patients had joint pain. Fatigue and sleep disorders had a percentage of 23.4%. Moreover, the patients who had stomachache were about 22.3%. Dizziness reported in about 19.1% of the patients. 18.1% of the samples had constipation. 13.8% suffered from nausea and sore throat. In addition, flu, urinary tract infection, muscle cramps, depression were adverse effects seen in percentage of 7.4%, 3.2%, 3.2%, 2.1%, respectively. This study confirmed the relation between the dose of RV and incidence of side effects, all adverse effects were more among patients who used 20 mg dose.

Conclusion:

All RV tablet products which are available in the Palestinian market passed the visual and pharmacopeial quality control tests. The effectiveness

and safety of these RV products were clinically convenient, however any unfavorable results related to the safety and efficacy of these products must be related to individual patient's factor not to the manufactured product.

Chapter One
Introduction

1.1 Background

1.1.1 Dyslipidemia

a) Global prevalence of dyslipidemia

Hypercholesterolemia is a disease characterised by high cholesterol levels in the blood circulation due to elevated lipid biosynthesis in the liver or over-consumption of foods with a relatively high cholesterol content, mainly from animal sources. Examples of high fat content foods are red meat, dairy products as well as egg yolks. According to the World Health Organisation (WHO), the global prevalence of hypercholesterolemia among adults in 2008 is 39%, and one of every three cases of ischaemic heart disease is related to elevated cholesterol levels in the blood. (1, 2)

Dyslipidemia clinically includes increased total cholesterol, triglycerides, low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol levels in the blood. The clinical significance of hypercholesterolemia arises from the fact that it is the major factor to cause cardiovascular diseases such as atherosclerosis and coronary heart disease, which increases the incidence of morbidity and mortality. According to the WHO, about 2.6 million deaths annually occur due to hypercholesterolemia. (2, 3)

According to the National Cholesterol Education Program, Adult Training Program III (NCEP, ATP III), in their final report, the desired total cholesterol level is less than 240 mg/dl, triglycerides (TGs) less than 200 mg/dl, low density lipoproteins (LDL) less than 160 mg/dl, and high density lipoproteins (HDL) more than 40 mg/dl.

b) Prevalence of dyslipidemia in Palestine

In 2019, a study conducted to assess the prevalence of dyslipidemia among undiagnosed Palestinian men aged between 24 and 60 years found a prevalence of 66.4%. The prevalence of elevated total cholesterol levels was 3.6% and high LDL was 8.5%. Moreover, the percentage of hyper TG was 20% and hypo HDL was present in 59.3% of participants. (4)

1.1.2 Statins

Cholesterol biosynthesis in the liver is catalysed by an enzyme called HMG-CoA reductase, which converts HMG-CoA to mevalonate. Statins act on this enzyme and inhibit it, which leads to a decrease in intracellular cholesterol levels and enhanced clearance of LDL cholesterol. As a result, the morbidity and mortality of cardiovascular diseases such as heart attack and stroke have been reduced. Statins include six approved drugs that are available on the market: pravastatin, fluvastatin, pitavastatin, atorvastatin, simvastatin and RV. (5)

Statins reduce LDL levels by 30-63% and TG by 20-40%; they also positively affect the levels of HDL by approximately 5%, depending on the

specific statin and dose. The results of a previous study on statins concluded that a reduction in LDL levels in the blood by 1 mmol/L leads to a 22% reduction in the incidence of cardiovascular diseases like myocardial infarction, coronary heart disease and stroke. (6)

The American College of Cardiology and the American Heart Association (ACC-AHA) cholesterol management guidelines have included statins as first-line therapy in adult patients who have high risk of atherosclerosis and cardiovascular disease. (7)

Statins in general cause several adverse events, including liver toxicity which is rare, increasing the risk of diabetes by approximately 20-30%. Neurological side effects are common and occur frequently, because statins are lipophilic agents and can cross the blood brain barrier. The most common side effects are muscle pain (myalgia), rhabdomyolysis and proteinuria that may lead to kidney disease. (5)

1.1.3 Rosuvastatin

Rosuvastatin (RV) is chemically (E,3R,5S)-7-[4-(4-fluorophenyl)-2-[methyl (methylsulfonyl) amino] -6- propan -2- ylpyrimidin -5- yl] -3, 5-dihydroxyhept-6-enoic acid, the molecular formula is $C_{22}H_{28}FN_3O_6S$ (Figure 1.1). It was approved for medical use in 2003. RV calcium is slightly soluble in water, freely soluble in methylene chloride and practically insoluble in anhydrous ethanol. RV is considered one of the most potent statins, it is used to reduce plasma cholesterol levels

(hypercholesterolemia) and for the prevention of cardiovascular diseases in combination with exercise, diet and weight loss. The absolute oral bioavailability of RV is approximately 20% and the elimination of RV and its metabolites is mainly by excretion in the faeces (about 90%). (8, 9)

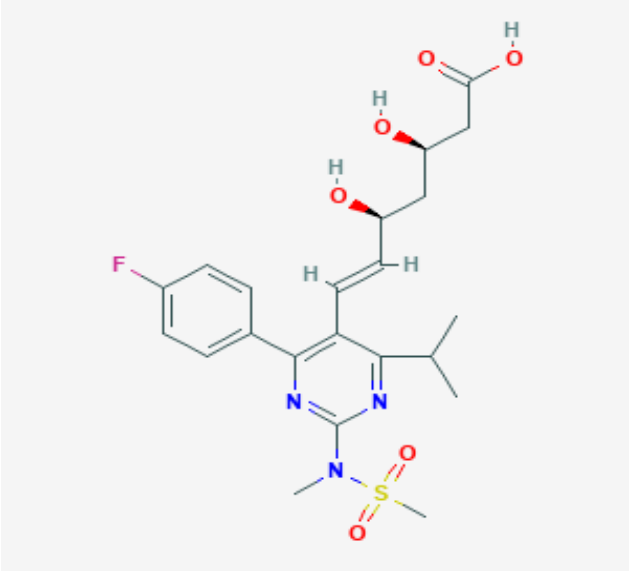

Figure 1.1: Chemical structure of RV**.** (9)

RV is hydrophilic agent metabolized by CYP2C9. After oral administration, it shows rapid absorption and the time to reach the (Cmax) is about 3 hours. RV has a long half-life of approximately 20 hours, so taking this medication is not affected by the time of day. Morning or evening drug administration provide the same efficacy in reducing LDL levels with a low incidence of side effects like myopathy.(10)

To meet the individual needs of patients and according to their blood cholesterol levels, RV tablets are available in different doses (5 mg, 10 mg, 20 mg and 40 mg) to meet the desired therapeutic need of patients. In Palestine, RV is tablets are available in only two doses,10 mg and 20 mg.

The recommended initial dose of RV for high blood cholesterol (hyperlipidaemia), hypertriglyceridemia and type III hyperlipoproteinemia is 10 mg to 20 mg orally once a day, and the maintenance dose is 5 mg to 40 mg orally once a day. **(Table 1.1.).** (11)

Table 1.1: RV tablet products available in the Palestinian pharmaceutical market.

Product name	**Liprose**	**Rosulip**	**Crestor**	**Rosuvastatin**	**Rovatin**
Manufacturing company	Pharmacare	*BPC	AstraZeneca	Teva	**JePharm
Year of Registration at Palestinian MOH	8.5.2016	24.6.2012	13.8.2005	23.12.2018	9.7.2019

*BPC: Birzeit Pharmaceutical Company

**JePharm: Jerusalem Pharmaceuticals

1.1.4.Pharmacovigilance

WHO defines pharmacovigilance or post-marketing surveillance as the science and activities relating to the finding, estimation, understanding and prevention of side effects or any other problems related to a drug. (12) Pharmacovigilance is important to assess the safety and efficacy of drugs, which helps pharmaceutical companies to follow-up on the effect of the medication after being on the market. In addition, if there are any serious adverse effects noticed in patients that were not found during clinical trials, the company can withdraw the medication from the pharmaceutical market before the drug can cause toxic effects in a large number of patients.

Pharmacovigilance is considered to be a legal requirement for pharmaceutical companies in many countries around the world; without pharmacovigilance, the company is not allowed to manufacture or market medications. So, pharmacovigilance is very important in pharmaceutical sciences to provide a full understanding of drugs that are already on the market in order to enhance the effectiveness of treatment, increase the safety of patients and to improve clinical outcomes. (13) Post-marketing studies are essential for all marketed drugs, especially narrow therapeutic medications and highly toxic drugs like anticancer therapies. (14)

Post-marketing studies face some barriers as they require a funding, a large number of participants who take the medication under certain criteria and physicians who to interview patients in the clinic to ask them about the treatment; thus, these studies take several years, which makes this kind of study less popular. Therefore, the effectiveness and safety of drug products are evaluated by using other types of studies that are less expensive and can be conducted within a short period of time. These studies include *in vitro* post-marketing surveillance. (15)

In the case of medications that have unclear risks and benefits or in case of the possibility of unexpected adverse events, the United States Food and Drug Administration (FDA) has the right to request companies that produce pharmaceutical products to submit Risk Evaluation Mitigation Strategies (REMS), in turn to emphasise the safety and effectiveness of medications and to evaluate the side effects presented as a result of taking

these drugs. Similarly, the WHO created a program called the WHO pharmacovigilance program. In 2010, approximately 134 countries joined this program, including the United States of America (USA) and European Union (EU). (14)

According to the WHO in 2019, only 45% of the 22 Arab countries are full members of the WHO Collaborating Centre for International Drug Monitoring, including Jordan, Egypt, Tunisia, Morocco and Saudi Arabia, which are considered to be advanced pharmacovigilance countries. On the other hand, about 31% of Arab countries are associate members and still in the early stages of pharmacovigilance programs, like Lebanon, Libya and Yemen. Some Arab countries are not members and have no pharmacovigilance systems in place, such as Palestine, Djibouti, Somalia and Mauritania. (16)

In Palestine, in 2016, a study was conducted to assess the attitude and knowledge of pharmacists who worked in community pharmacies and hospital pharmacies about pharmacovigilance and adverse drug reactions (ADR). The knowledge and ability of hospital clinical pharmacists to define pharmacovigilance and ADR correctly was higher than community pharmacists. However, in general, Palestinian pharmacists have a low level of knowledge about pharmacovigilance.(17)

Studies about statins in general and RV in specific are many, but there are few studies on the pharmacovigilance of pharmaceutical products throughout the world. Unfortunately, in Arab countries, this kind of study

is limited; thus, we need studies on the pharmacovigilance of medications to provide a full understanding of drugs available on the market to enhance the effectiveness of treatment, increase the safety of patients and improve clinical outcomes.

To the best of our knowledge, there are no studies in Arab countries and especially in Palestine concerning the pharmacovigilance of RV. As a result, this study was conducted for the purpose of testing *in vitro* and *in vivo* post-marketing surveillance of RV in patients administered different products containing RV within the Palestinian community. Additionally, different products containing RV available in the Palestinian market were collected and analysed in terms of assay and content uniformity to assess the quality of their pharmaceutical manufacturing.

1.2 Objectives

1. To evaluate the safety and efficacy of different RV products.
2. To assess the pharmaceutical quality control of common RV products.
3. To test the *in vivo* post-marketing surveillance of RV among Palestinian population.
4. To test the *in vitro* post- marketing surveillance of RV products.

1.3 Significance of the study

1. This study will help to establish a complete knowledge of the drug RV from a pharmacovigilance point view.

2. Results of this research can be used to optimize safety and efficacy during RV treatment as well as improving clinical benefits and outcomes.

3. Assessment of various generic names and products that contain RV in terms of pharmaceutical quality.

Chapter Two

Literature Review

A previous study was performed to assess the influence of hepatic impairment on RV pharmacokinetics and pharmacodynamics. Participants were men and women with mild hepatic function, moderate hepatic function and normal hepatic function, they were given oral dose of RV once daily for two weeks, during this period blood and urine samples were collected for RV assay. The results revealed that the pharmacokinetics of RV in subjects with mild hepatic function and moderate hepatic function was identical to subjects with normal hepatic function, and the percentage of LDL reduction is similar between them. (18)

In 2007, a study was conducted in England to assess the post-marketing safety of RV taken by a number of patients in primary care. It concluded that RV is well tolerated; however, the most common adverse event of the drug which leads to discontinuation of the therapy was myalgia, and using a high dose of 40 mg/day lead to abnormal liver function tests (LFT) about 2.5 fold more than the dose of 10 mg/day. (19)

In 2016, a previous post-marketing study on patients who has coronary artery diseases in India evaluated the clinical safety and efficacy of RV 40mg once daily in treating dyslipidemia, the results revealed that RV significantly decrease LDL cholesterol with lower incidence of adverse effects. (20)

In Canada, in 2013, a study was conducted to estimate the relation between using statins and the onset of diabetes mellitus. Patients who enrolled in this study were not diabetic. They were then given different statin agents like atorvastatin, RV, simvastatin, fluvastatin and pravastatin. The result was a rise in the risk of new onset of diabetes mellitus due to the use of high potency statins such as atorvastatin and simvastatin. (21)

In 2015, a study was conducted in America to compare between RV and atorvastatin among patients who have acute coronary syndrome (ACS). RV 20mg and atorvastatin 80mg had similar safety profile and efficacy in decreasing LDL levels in the blood. The study also showed that RV 40mg was more effective than atorvastatin 80mg in lowering LDL level and significantly raising the level of HDL . In addition, RV provided safety profile better than atorvastatin with low incidence of major adverse events such as liver toxicity. (22)

A previous study was made in 2001 to compare between pravastatin, simvastatin and RV, 205 patients were enrolled in this study and treated with RV 5mg and 10mg, pravastatin 20mg and simvastatin 20mg for 12 weeks. After this period, blood samples were collected to check the levels of total cholesterol, LDL , TG and HDL. It resulted that RV in both doses was more potent than pravastatin and simvastatin in reducing LDL level and total cholesterol level. Moreover, it more significantly affected HDL level. (23)

In the United States of America (USA), in 2015, a study was made to determine the differences in RV pharmacokinetic between Asian subjects and Caucasian subgroups. It revealed that there are significant differences in RV pharmacokinetics such as the maximum plasma drug concentration which was in Asian subgroups higher about 70-98% than Caucasians who are living in the same environment. (24)

In Jordan, in 2016, a study was conducted to determine the differences in RV pharmacokinetic between Asian, Caucasian and Arab subgroups. Thirty Participants were enrolled in this study, they were given the two dosage forms of RV. The results showed that the pharmacokinetic parameters of RV such as the maximum plasma drug concentration among Arab and Caucasian subjects were identical, whereas Asian subgroups showed higher plasma drug concentration. (25)

In 2002, a study was conducted to assess the effect of gender and age on the pharmacokinetics of RV. A 32 healthy males and females in various ages were included and the mean of ages for young was 24 years and for elderly was 68 years. They were given a single oral dose of RV 40mg and it was found that there is a small difference in RV pharmacokinetics based on age and gender with the same safety profile between young and elderly men and women volunteers; so there is no need to adjust the dose of RV according to age or gender. (26)

In 2012, in Japan, a study was conducted to assess the efficacy of RV at low dose of 2.5mg in reducing the risk of atherosclerosis and coronary artery diseases in postmenopausal women who have the LDL level 140mg/dl or higher. The results showed that statins have a significant role in postmenopausal women with low risk of dyslipidemia in reducing the risks of cardiovascular diseases such as atherosclerosis and coronary artery diseases. (27)

In 2013, a study aimed to evaluate the efficacy of changing the treatment for mixed dyslipidemia, which is characterized by high LDL cholesterol level, high triglyceride level and low HDL cholesterol level. Patients who enrolled in this study used a standard dose of statin but it wasn't sufficient to treat mixed dyslipidemia. The therapy was switched to a new management, which included RV at the highest approved dose 40mg, added fenofibrate or nicotinic acid extended release formula for a period of three months. Results showed that switching to new management of using RV at the highest dose 40mg and adding nicotinic acid is better in reducing LDL cholesterol level and triglyceride and raising HDL cholesterol level than adding fenofibrate. (28)

In 2016, in Palestine, a study was made to assess the safety and efficacy of valsartan using in vitro and in vivo post-marketing surveillance that included hypertensive patients. The results revealed that all valsartan drug products available in Palestinian pharmaceutical market are of high quality and within the international requirements. In addition, valsartan

products were well tolerated and mild to moderate adverse effects occurred, the most frequent one is headache. (15)

A previous study was made in 2010 to describe pharmacovigilance programs in 55 countries with low and moderate income and to recognize the most important pharmacovigilance priorities. In many of the low and moderate income countries still the pharmacovigilance is a relative new concept, and pharmacovigilance activities should use the adverse events information in better way leading to contribution in a more evidence based process to treatment guidelines. (29)

In Korea, in 2017, a study was conducted to evaluate the safety and expected adverse drug reactions of statins among patients with dyslipidemia through a certain period, from July 2009 to June 2014, of treatment with statin products available in Korea like; RV, simvastatin, atorvastatin, fluvastatin and pitavastatin. This study presented the importance of pharmacovigilance to detect the adverse drug reactions of medications which are already found in the market. The results showed that atorvastatin reported the highest percentage of other statins to cause adverse drug reactions. Moreover, the most common side effects of statins were gastrointestinal disturbances like dyspepsia and musculoskeletal disorder such as mayalgia. (30)

High-performance liquid chromatography (HPLC) is an analytical method used to separate, distinguish, and measure each ingredient in a mixture. In 2010, a study was conducted to develop a simple, accurate,

reliable, satisfactory and validated HPLC method for the assay of RV and to test the content uniformity of RV pharmaceutical products. This HPLC instrumental analysis was shown to be effective and validated according to the United States Pharmacopeia (USP) requirements for evaluation of the assay of RV and the test of the content uniformity of RV pharmaceutical products. Furthermore, this method was able to distinguish RV from other degradation products resulted due to various stress conditions. (31)

Chapter Three
Method

3.1 *In vitro* post-marketing quality control study

3.1.1 Chemicals and reagents

USP RV calcium reference standard was provided by Pharmacare PLC (Ramallah, Palestine). Samples of all four generic RV products (10 mg and 20 mg tablet formulation) available in the Palestinian pharmaceutical market were purchased from a local pharmacy. The batch numbers, manufacturing license numbers and the date of production and expiration of the purchased products were inspected. Solvents such as methanol and acetonitrile (High-performance liquid chromatography grade) were purchased from Sigma-Aldrich (German). Other chemicals and reagents used in this study; phosphoric acid, potassium dihydrogen phosphate and sodium citrate were of HPLC grade and were purchased from Sigma-Aldrich. Moreover, the water used in the analysis was water for HPLC from Honeywell (German) and the Milli-Q plus water purification system from Veolia water (Paris, France) was also used to prepare high purified water. All other reagents were of HPLC grade.

Table 3.1: Chemicals and Reagents.

Chemicals and reagents
RV calcium powder.
RV tablet products.
Methanol.
Acetonitrile.
Phosphoric acid.
Potassium dihydrogen phosphate.
Sodium citrate.
Water for HPLC.

3.1.2 Instrumentation and techniques

High-performance liquid chromatography:

High-performance liquid chromatography (HPLC) is an analytical method used to separate, distinguish, and quantify each ingredient in a mixture. The HPLC system used in this study is 1525 Binary HPLC Pump from Waters, with 2 to 4.6 mm I.D. columns for liquid chromatography (LC) and liquid chromatography/ Mass spectrometry (LC/MS) applications and flow-rate range of 0.00 to 10.00 mL/min in 0.01 mL increments. In addition, this HPLC system consisted of 1500 series column heater to maintain precise and appropriate column temperature in the range of 20 to 60 °C.

Dissolution apparatus:

Dissolution tests provide an in-vitro simulation to test the rate and extent of drug release from various drug formulations, for example capsule and tablet, which gives a critical data about the efficacy and bioavailability

of the drug formulation. In this study, the dissolution machine used was from Hsiang Tai machinery industry company which is in Taiwan, China. This type of dissolution tester is Dissolution Apparatus 2 Paddle, which consists of six vessels each of them has a volume about 900 ml of dissolution media and speed of the paddle is between 10 – 220 rpm.

Table 3.2: Instruments and Tools.

Instruments and tools
HPLC.
Dissolution apparatus.
Disintegration apparatus.
Analytical weighing balance.
Hardness tester.
SPSS.

3.1.3 Selection of commercial products

Five different brands and generic products of RV were available in the Palestinian market as shown in **Table (1.1)**. Four of these products each having two strengths of 10mg and 20mg were included in this study as one of the products was available in the pharmaceutical market after we collected the data and it was not enrolled in this study.

3.1.4 Pharmaceutical Quality Control

Most RV coated tablets which are available in Palestine were visually inspected for general appearance such as color, shape, or any undesired coating defect such as blooming, orange peel, blushing, pitting,

etc.. In addition, other pharmacopeial quality control tests were performed to assure pharmaceutical quality of these tablets including hardness of the tablet, weight uniformity, assay, disintegration time and dissolution profiles.

3.1.4.1 Assay

The assay of RV products was assessed in compliance with the USP. The mobile phase was a mixture of 400 ml of 0.02 M potassium dihydrogen phoasphate in milli Q water, 300 ml acetonitrile and 300 ml methanol, the pH of the mobile phase was adjusted to 4 with phosphoric acid then it was filtered through 0.45 micro membrane filter.

To prepare the standard solution, 26 mg of RV calcium was weighed and dissolved in 50 ml of the diluent (a mixture of acetonitrile and water), the mixture was sonicated for about fifteen minutes until the powder completely dissolved. Then 4 ml from this solution was transferred to 50 ml volumetric flask and diluted to the volume using the mobile phase. To prepare the sample, twenty tablets from each strength of the RV products were smashed using mortar and pestle into a very smooth powder. An equivalent quantity about 41.668 mg of RV calcium powder was weighed and dissolved in 100 ml of diluent, the solution was sonicated for about thirty minutes until the powder completely dissolved. Then 5 ml of the supernatant was transferred to 50 ml volumetric flask and diluted with mobile phase to volume. A portion of the final solution was passed through a nylon-membrane filter having a 0.45 μm filter and the first 10 ml of the

filtrate were rejected. The filtered sample was injected by volume of 20 µl into the HPLC and passed through the column (C18 5µm, 4.6*250mm cartridge and UV wavelength 248 nm) at 0.8 ml/min. The percentage of the RV content in the pharmaceutical products compared to the standard was calculated using the following equation:

$$\% \text{ of } RV = \left(\frac{ru}{rs}\right) * \left(\frac{Cs}{Cu}\right) * STD \text{ Potency } (\%)$$

Where:

ru: Peak area response of the sample solution.

rs: Peak area response of the standard solution.

Cs: Concentration of the standard solution (µg/ml).

Cu: Concentration of the sample solution (µg/ml).

Potency: 96.8 %.

3.1.4.2 Weight uniformity test

To evaluate the weight uniformity of RV tablets, twenty tablets from each of the four products of RV in both strengths (10 mg and 20 mg) were randomly picked out and weighed individually using an analytical weighing balance. According to USP test for weight uniformity, the average weights for each RV products was calculated, and the percentage of each tablet compared to the average weight should be within the limit, ±7.5% of the average weight for tablets weighing between 80mg and 250mg and ±5% of the average weight for tablets weighing more than 250mg.

3.1.4.3 Hardness and friability

The purpose of hardness test is to assess the crushing strength of RV tablet products, 10 tablets of each product were randomly selected to measure the hardness using the hardness tester. Furthermore, friability test was not done because the RV tablet product were coated tablet, so there is no need for friability test.

3.1.4.4 Disintegration

To assess the disintegration time of RV products, six tablets from each product were placed in a disintegration apparatus which consists of a basket with six tubes, the base of each tube has a 10-mesh screen. The basket loaded with the tablets was immersed in a bath of water and the temperature was 37°C. The disintegration time of the tablets was noted when each tablet completely disappeared and no particles stacked on the mesh of the basket of the disintegration tester.

3.1.4.5 Dissolution

To assess the dissolution of RV tablet products, a standard solution was prepared which was used to establish the different RV products dissolution profile, 29 mg of RV calcium were weighed and dissolved in 50 ml of diluent (a mixture of acetonitrile and water 50:50), the mixture was sonicated for about fifteen minutes until the powder completely dissolved, completed to 100 ml volume using dissolution medium (0.05 M sodium citrate buffer, pH 6.6), then 4 ml of the standard stock solution was diluted

to 100 ml with the dissolution media. To prepare the sample solution, six tablets from each product were tested using USP Dissolution Apparatus 2 Paddle, 900 ml of dissolution medium was placed in each vessel of the apparatus and the temperature was equilibrated at 37 ± 0.5 C. One tablet of each RV products was placed in each of the dissolution vessels with a paddle stirrer at 50 rpm. At the end of 30 minutes, sample aliquots (5 ml) were withdrawn from a zone midway between the surface of the dissolution medium and the top of the rotating paddles, filtered through a nylon-membrane filter 0.45 micron. The filtered sample was injected by volume of 20 µl into the HPLC and passed through the column (C18 5µm, 4.6*250mm cartridge and UV wavelength 248 nm) at 0.8 ml/min. The percentage of the RV content in the pharmaceutical products compared to the standard was calculated using the following equation:

$$\%\ of\ RV = \left(\frac{ru}{rs}\right) * \left(\frac{Cs}{Cu}\right) * STD\ Potancy\ (\%)$$

ru: Peak area response of the sample solution.

rs: Peak area response of the standard solution.

Cs: Concentration of the standard solution (µg/ml).

Cu: Concentration of the sample solution (µg/ml).

Potency: 96.8%.

3.2 *In vivo* post-marketing surveillance study

3.2.1 Study design

The study was conducted in an internal clinic at An-Najah hospital in Nablus for a period of 6 months, observational, *in vivo* post- marketing surveillance study designed and approved by the local ethics committee (Institutional Review Board [IRB] of An-Najah National University). (Appendix 1)

At this stage of the study, the primary objective was to assess the effectiveness of RV treatment among Palestinian patients with dyslipidemia. The secondary objective was to collect an evidence based prevalence of the side effects that appears as a result of treatment with RV products.

3.2.2 Population

Patients chosen for this study were previously diagnosed with dyslipidemia (total cholesterol level > 240mg/dl, LDL >160mg/dl, TG >200mg/dl or HDL <40mg/dl) and they were at the age of 18 years or older. This study excluded patients with a history of malignancy in the previous years, pregnant or breastfeeding women, or with known hypersensitivity to RV or any ingredients in the formulation.

3.2.3 Data collection form

A Self-administered questionnaire in the native Arabic language was used after the participants had agreed to participate (verbal consent form).

The questionnaire consisted of three parts : (Appendix 2)

1. The first section consisted of questions on sociodemographic and other background data (age, gender, education levels, living place, monthly income, social status and others).

2. The second section included questions about the patient's medical history and if they use any medications other than RV.

3. The third section covered any possible adverse effects noticed after taking RV.

3.2.4 Data collection procedure

The Data collection was carried out in a face-to-face interview during which we asked patients with dyslipidemia to fill in the questionnaire. A verbal consent forms explaining the purpose of the research and assuring confidentiality was read to participants. The participants had all rights whether to participate or not. The participation was voluntary not mandatory.

3.2.5 Ethical consideration

The Institutional Review Boards (IRB) before the initiation of this study (Appendix 1) authorized all aspects of the study protocol. Verbal consent was also obtained from the participants prior to the commencement of the study. We confirm that the collected data is used for clinical research only. The provided information is confidential and has not been used for any other purposes than the study. No one except the researchers had access to information and data.

3.2.6 Treatment and assessment

At the first visit, the participants were asked to fill the questionnaire, the physician asked the patients to make a test to check the level of total cholesterol, LDL, TG and HDL then the physician prescribed RV for these patients, the dose was chosen according to the cholesterol level and other lab tests. After one month the participants came back to the clinic to report any adverse events caused by the medication and they were checked for the level of total cholesterol, LDL, TG and HDL.

The effectiveness of RV was evaluated from the improvement in the lab tests and the decrease in cholesterol level, LDL level, TG level as well as the increase in HDL levels compared to the initial lab results and after one month of treatment.

Moreover, the evidence of side effects of RV products was evaluated according to the participant's answer to our question: "Did you complain from any of the following side effects?"

3.2.7 Statistical analyses

All data was coded, entered and analyzed by SPSS V21 statistical computer program (SPSS Inc., Chicago, IL, USA). Mean ± standard deviation was computed for continuous data. Frequencies and percentages were calculated for categorical variables. Probability (p) value of less than 0.05 was considered to be statistically significant for all analyses.

Chapter Four
Results

4.1 *In-vitro* post-marketing surveillance

4.1.1 Visual analysis

Four different products containing RV available on the Palestinian pharmaceutical market (F1, F2, F3, F4), at doses of 10 mg and 20 mg, were checked for their appearance and organoleptic properties, which are illustrated in **Table 4.1**. The colour of all products was pink, and the shape of the tablet was spherical and oblong for 10 mg and 20 mg, respectively. In general, the quality of the tablets was good and there were no obvious marks of abnormalities or disorders in the shape and colour or any signs of unusual spots on the products which were tested. In addition, no signs of blooming, orange peel, blushing, pitting or any other coating defects were observed in any of the tested tablets. (32)

The batch numbers, the date of production and expiration of the purchased products were inspected as mentioned in the **Table 4.2**.

Table 4.1: Visual analysis of RV tablet 10 mg and 20 mg

Appearance and organoleptic properties	Result
Color	Pink
Shape	Spherical for 10 mg and oblong for 20 mg
Coating defects	No signs of blooming, orange peel, blushing or pitting

Table 4.2: Industrial data.

	Batch number		Manufacturing date		Expiration date	
Dose	**10 mg**	**20 mg**	**10 mg**	**20 mg**	**10 mg**	**20 mg**
F1	PT252	PR896	5/2018	6/2018	4/2021	5/2021
F2	R73042	R74043	9/2017	3/2018	8/2020	2/2021
F3	172800	182685	11/2017	9/2018	5/2020	3/2021
F4	90G18	83L18	8/2017	11/2017	7/2020	12/2020

4.1.2 Weight uniformity

As the weight uniformity of the RV tablets was estimated, all products were within the USP weight uniformity test, the average weight of the first formulation (F1) was 154.14 mg and 308.12 mg for the dose 10 mg and 20 mg respectively. The second formulation (F2) the average weight of 10 mg was 156.67 mg and 314.09 mg for the 20 mg dose. The average weight of the third formulation (F3) was 166.83 mg and 326.69 mg for 10 mg and 20 mg respectively. For the fourth formulation (F4) the average weight of the 10 mg strength was 189.89 mg and 371.89 mg of the 20 mg strength formulation. All the RV tablets was around 166 mg and 330 mg

for strength 10 mg and 20 mg respectively and within the limit according to USP. Results of weight uniformity test for RV tablets are illustrated in **Table 4.5** and **4.6.**

4.1.3 Hardness and friability

Regarding the hardness of the tested RV tablets, the maximum and the minimum levels were 103.5 N and 69.8 N, respectively, with a mean of 91. The accepted range is between 50-120 N. Moreover, the disintegration time of all RV products was within the range of 2-3 minutes.

4.1.4 Assay

The assay of RV in the four commercial products chosen from the Palestinian pharmaceutical market was evaluated with respect to an RV standard according to the HPLC method mentioned above. The concentration of the RV standard was 0.0416 mg/ml and the concentration of the sample was 0.041668 mg/ml. All samples of RV tablet products were prepared and analysed by HPLC; one main peak for RV appeared after about 13 min on average. Each formulation was injected into the HPLC three times and the average of the area under the curve was used in the equation. The first formulation F1 at the 10 mg dose was prepared and injected into the HPLC; the area under the curve of the peak was 4439873 and the percentage of the drug content in this formulation was 108.3%. The 20 mg dose of the same product showed a peak with an area of 4477871; the amount of RV in it compared with the standard was 109.2%. The

second formulation F2 10 mg dose was also prepared and injected into the HPLC, resulting a single peak with an area of 4361487; the amount of the product was 106.4%. The area under the curve for the 20 mg dose of this formulation was 4238733 and the drug content in the tablet was 103.4%. The third sample F3 was tested using HPLC; the area under the curve was 4407363 and 4417348 for the 10 mg and 20 mg doses, respectively. The results from HPLC were applied to the equation to calculate the amount in each dose, which was 107.5% and 107.77% for 10 mg and 20 mg, respectively. The fourth and last RV tablet product F4 was also prepared and analysed by HPLC. The area of the peak of the 10 mg dose was 4032186 and that of the 20 mg dose was 4267478. The amount of RV in each dose was calculated according to the RV standard; the amount was 98.38% for the 10 mg dose and 104.12% for the 20 mg tablet. Assay results of the 10 mg and 20 mg RV tablet products are mentioned in **Table 4.5 and Table 4.6** respectively.

4.1.5 Dissolution

All the tested RV products showed a full release of the active ingredient RV within 30 minutes in dissolution media at pH 6.6, which was prepared according to the process described in the Methods. The RV standard was prepared and analysed by HPLC, the concentration of which was 0.0116 mg/ml. The samples of RV tablet products containing 10 mg of the drug were prepared according to the procedure mentioned in the Methods section to a concentration of 0.0111 mg/ml, then injected into the

HPLC. Each sample was injected into the HPLC three times and the average of the area under the curve was used in the equation. The first sample F1 was analysed by HPLC with an area of the peak of 1295959; the percentage of the drug after dissolution compared with the standard was 105.3%. The second product F2 was analysed by HPLC and the area under the curve was 1063006; the percentage of dissolution was 86.37%. The third RV tablet product F3 had an area of the peak of 1197313 and the dissolution result was 97.28%. The last sample F4 was analysed by HPLC; the area of the peak was 1341090 and the percentage of dissolution result calculated by the equation mentioned above was 108.96%. **Table 4.3** illustrates the AUC and dissolution results after 30 minutes for the 10 mg RV tablet products.

Regarding the RV tablet products at the 20 mg dose, the samples were prepared at concentration of 0.0222 mg/ml. The area under the curve of the first sample F1 was analysed by HPLC with an area of the peak of 2370979; the percentage of the dissolution compared to the standard was 96.32%. For the second formulation F2, the area of the peak was 2504415 and the dissolution result was 101.74%. The third RV tablet product F3 was analysed by HPLC; the area of the peak of the sample was 2436592 and the percentage of the dissolution was 98.99%. The fourth product F4 was dissolved in dissolution media, then analysed by HPLC; the area under the curve was 2206057 and the percentage of dissolution of this sample compared to the standard was 89.62%. **Table 4.4** illustrates the AUC and the 30 minutes dissolution assay results for the 20 mg RV tablet products.

Table 4.3: Dissolution results after 30 minutes of the 10 mg RV tablet products.

	Standard RV	F1	F2	F3	F4
Average AUC	1244989	1295959	1063006	1197313	1341090
SD	94869.2	94491.73	91498.35	118229.3	81746.31
RSD	7.620084	7.291259	8.60751	9.874556	6.095513
%Dissolution	100%	105.3%.	86.4%	97.3%	109.0%.

Table 4.4: Dissolution results after 30 minutes of the 20 mg RV tablet products.

	Standard RV	F1	F2	F3	F4
Average AUC	1244989	2370979	2504415	2436592	2206057
SD	94869.2	77643.89	95321.83	55655.17	164859
RSD	7.620084	3.274761	3.806151	2.28414	7.473018
%Dissolution	100%	96.3%	101.7%	99.0%	89.6%

Table 4.5: Summary of quality control tests of RV tablet 10 mg

	F1	F2	F3	F4
Assay %	108.3%	106.4%	107.5%	98.4%
Dissolution %	105.3%	86.4%	97.3%	109.0%
Wt uniformity (mg)	154.14	156.67	166.83	189.89

Table 4.6: Summary of quality control tests of RV tablet 20 mg[1]

	F1	F2	F3	F4
Assay %	109.2%	103.4%	107.8%	104.1%
Dissolution %	96.3%	101.7%	99.0%	89.6%
Wt uniformity	308.12	314.09	326.69	371.89

According to the prices of RV tablet products available in the Palestinian pharmaceutical market, the brand RV (F1) was more expensive than the three generic RV tablet products (F2, F3 and F4). The price differentials of RV tablet products are in **Table 4.7**

Table 4.7: Price difference of RV tablet products in JD.

	10 mg	20 mg
F1	18.21	26.67
F2	13.23	21.9
F3	16.26	23.85
F4	14.53	21.46

The most prescribed RV tablet product was the generic RV (F1), about 38.3% of patients used it. In addition, the results showed the generics RV tablet products F3 and F4 were equally prescribed about 27.7%. Concerning the release of RV from the tablets, the generic tablet products were identical regarding to the brand RV tablet product. The frequency and percentage of RV tablet products prescribed are shown in **Table 4.8**.

[1] There was no need to calculate similarity and non similarity factors since the prescribed products showed release higher than 85% within 15 minutes in all dissolution mediums recommended for in vitro in vivo prediction (1.2, 4.6, and 6.6).

Table 4.8: Frequency and percentage of RV tablet products prescribed

	Frequency	Percent (%)
F1	36	38.3
F2	6	6.4
F3	26	27.7
F4	26	27.7
Total	94	100

4.2 *In vivo* post-marketing surveillance

4.2.1 Socio-demographics

Demographic information of the subjects are presented in **Table 4.9**. Ninety-four questionnaires were collected from the internal medicine clinic at An-Najah hospital in Nablus. Respondents were mainly female (55.3%). The age distribution was 27-83 years; the mean age of respondents was 53.266 years with a standard deviation of ± 14.05 and a median of 54.00 years. Regarding educational levels, the highest percentage was for a primary education, followed by a university education (35.1% and 29.8%, respectively). More than half of the respondents (55.3%) were living in a city while 35.1% of them were living in a village. The dominant income level of the participants was on average about 600-1000 Jordanian Dinar (JD).

The majority of the participants were using other medications in addition to RV (81.9%). Furthermore, RV treatment showed that 37.2% of

patients were prescribed the dose of 10 mg and the percentage of patients who were prescribed RV at a dose of 20 mg was 62.8%.

Table 4.9: Demographic data of the samples.

Variable	Number (N=94)	Percentage (%)
Gender		
Male	42	44.7%
Female	52	55.3%
Age (years)		
20 – 29	3	3.2%
30 – 39	17	18.1%
40 – 49	15	16%
50 – 59	25	26.6%
60 – 69	20	21.3%
70 – 79	13	13.8%
80 – 89	1	1.1%
Educational level		
Illiterate	3	3.2%
Primary	33	35.1%
Secondary	22	23.4%
University	28	29.8%
Higher education	8	8.5%
Residency		
City	52	55.3%
Village	33	35.1%
Palestinian refugee camps	9	9.6%
Other medications		
Yes	77	81.9%
No	17	18.1%

4.2.2 Assessment of the safety profile

RV and the statin family of compounds in general have a broad profile of adverse effects; however, most of them are mild to moderate. In addition, there were no critical adverse effects or cases of death recorded during the study. The most frequent adverse effect was muscle pain

(51.1%); about 48 of the participants suffered from it. The next side effect was headache; about 25 of patients had headache after using RV with a percentage of 26.6%. 24.5% of the included sample had joint pain, 22 of the respondents complained of fatigue and sleep disorders (23.4%) and 21 of the patients who were prescribed RV had stomach-ache (22.3%). Dizziness was reported in about 19.1% of the patients, and 18.1% of the sample had constipation due to RV use. About 13 respondents suffered from nausea and sore throat (13.8%). Moreover, flu, urinary tract infection, muscle cramps and depression were other adverse effects associated with RV treatment in 7.4%, 3.2%, 3.2% and 2.1% of the sample, respectively. All adverse effects were more common among patients who used the 20 mg dose; for muscle pain sore throat, and nausea, the difference was statistically significant, with P-values of 0.001, 0.018 and 0.018, respectively. Moreover, 79.2% of patients who had muscle pain used RV 20 mg, and 92.3% of participants who suffered from sore throat and nausea were treated with RV 20 mg. A list of the reported side effects and their incidence of occurrence are summarized in **Table 4.10**.

Table 4.10: Incidence of adverse effects of RV.

Adverse effect	Frequency (N=94)	Percentage (%)
Muscle pain	48	51.1
Joint pain	23	24.5
Sore throat	13	13.8
Headache	25	26.6
Nausea	13	13.8
Fatigue	22	23.4
Constipation	17	18.1
Dizziness	18	19.1
Stomachache	21	22.3
Flu	7	7.4
Urinary tract infection	3	3.2
Muscle cramps	3	3.2
Depression	2	2.1
Sleep disorders	22	23.4

4.2.3 Assessment of efficacy of RV treatment

RV is considered one of the most potent statins used to treat hypercholesterolemia. In this study, different brands of RV at both 10 mg and 20 mg were sufficient to produce a reduction in the level of total cholesterol, LDL and TG and increase the level of HDL. The statistical analysis showed that the mean total cholesterol, LDL, HDL and TG levels before treatment were 234.82, 162.65, 31.97 and 248.98, respectively. After three months using RV, the total cholesterol, LDL, HDL and TG levels were 154.41, 97.1, 44.61 and 159.67, respectively. **Table 4.11** levels of total cholesterol, LDL, HDL and TG before and after using RV treatment.

Table 4.11: Levels of total cholesterol, LDL, HDL and TG before and after treatment.

	Before treatment			
	Total cholesterol	**LDL**	**HDL**	**TG**
Minimum	140	67	20	150
Maximum	350	260	44	1500
Mean	234.8298	162.659	31.9787	248.989
Std. Deviation	41.94175	28.96366	5.9224	148.46719
	After treatment			
	Total cholesterol	**LDL**	**HDL**	**TG**
Minimum	70	54	30	50
Maximum	250	160	55	300
Mean	154.414	97.1064	44.617	159.67
Std. Deviation	31.16774	24.64914	5.09502	39.03442

Chapter Five
Discussion

RV considered one of the most potent statins, used to reduce plasma cholesterol levels (hypercholesterolemia). Many previous studies have shown that RV is more effective at reducing total cholesterol and LDL level than other statins like atorvastatin, pravastatin and simvastatin, with a lower incidence of adverse effects. (22, 23)

According to the bioavailability of RV, a study was conducted to assess the bioavailability of generic RV 20 mg produced by Jordanian drug companies and the reference RV product called Crestor 20 mg manufactured by AstraZeneca. Thirty volunteers were enrolled in this study, they were given the two dosage forms of RV. The results revealed that the test and reference RV products were bioequivalent, in which the rates and extent of absorption presented by the maximum plasma drug concentration for both RV products were equivalent. (25)

5.1 *In vitro* post-marketing surveillance

Our *in vitro* post-marketing surveillance estimation confirmed that all RV products that were included in this study and chosen from the Palestinian market are of high total quality as they all passed the required quality control tests that are generally performed on tablet dosage forms.

All products that are available locally on the Palestinian market containing RV were within United States Pharmacopeia (USP)

requirements. The acceptance value for the assay of RV tablet product is between 90-110% compared with the standard, and for dissolution this is between 85-115% compared with the standard. Regarding the dissolution rate, all RV products showed a complete release of the active ingredient RV within 30 minutes in the dissolution medium at pH 6.6. (33)

In the assay test, the amount of RV in the tested products available on Palestinian pharmaceutical market was evaluated and compared with the RV standard. The assay of all RV products was close to 100%.

At the beginning of this study, we performed a visual analysis of the RV tablet products to check for any coating defects, such as tablet discoloration, edge erosion, cracking of the coating or tablet breakage. The appearance of the tablet or any signs of coating defects play an important role in patient compliance; if the patient noticed any defects in the tablet, they would likely refuse take the medication. The results showed there were no signs of coating defects or any other abnormalities. In general, the quality of RV tablet products that were analysed in this study was good. (32)

5.2 *In vivo* post-marketing surveillance

The results from the clinical data of this study support the effectiveness of the different products of RV chosen from the Palestinian market within an accepted range. According to the adverse effects, the participants in this study complained from some side effects, as with other

statins. The most common side effect was muscle pain (myalgia) (51.1%). Importantly, patients who used RV 20 mg suffered from side effects more than those who used the other dose. In general, the incidence of side effects like myopathy, gastrointestinal disorders and other adverse effects caused by RV were less than with other statins. A previous study that compared statins showed that 48.4% of atorvastatin users reported adverse drug effects by this was only 23% in RV users. (30)

5.3 Strength and limitations of the study

There have been no studies in Arab countries and especially in Palestine concerning pharmacovigilance for RV. As a result, this study was conducted with the purpose of performing *in vitro* and *in vivo* post-marketing surveillance of RV in patients administered different products of RV within the Palestinian community. Five different products of RV, at both 10 mg and 20 mg doses, are available on the Palestinian market. One of the products was not included in the study because it was available in the pharmacies after the data was collected and at that time there were no patients using it.

RV products that are available on the pharmaceutical market are expensive related to other statin products like atorvastatin and simvastatin, so there is a smaller number of patients who use RV to treat hypercholesterolemia; only 94 patients were included in this study. In addition, this type of statin is not found in the Ministry of Health (MOH), so we could not collect patient samples from government clinics and

hospitals. The samples was collected only from the internal medicine clinic at An-Najah hospital. Regarding private clinics and hospitals, it is difficult to follow-up these patients after three months to evaluate the reduction in the levels of LDL, TG and total cholesterol, so the samples was not collected from them.

5.4 Conclusion

At the end of this study, the results showed that all RV tablet products that are available on the Palestinian market were close to 100% for all required quality control tests like assay, dissolution and disintegration. In addition, there were no differences between the branded product and the generic products containing the same dose of RV, and they showed the same efficacy in lowering the cholesterol levels and a similar safety profile. The most common side effect of RV was muscle pain. We conclude that the effectiveness and safety of these RV products are clinically convenient, so any unfavourable results related to the safety and efficacy of these products must be related to individual patient factors, not to the manufactured product.

5.5 Recommendations

Post-marketing surveillance is a term used to check the efficacy, safety and quality of pharmaceutical products that have been introduced to the market. In Arab countries, this kind of study is limited; thus, we need studies on pharmacovigilance of medications to provide a full

understanding of drugs that already existed on the market to enhance the effectiveness of treatment, increase the safety of patients and improve clinical outcomes.

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Appendices

Appendix (1)

An-Najah
National University
Health Faculty of medicine&
Sciences
IRB

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: PHC

IRB Approval Letter

Study Title:

"In vitro and in vivo post-marketing surveillance of Rosuvastatin among Palestinian patients"

Submitted By:
Nawras Radwany

Supervisor:
Dr. Abdel Naser Zaid , Dr. Rawa Alramahi

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28th Jan 2019

Date Approved:
26h Feb 2019

Your Study titled **"In vitro and in vivo post-marketing surveillance of Rosuvastatin among Palestinian patients"** with archived number (20) February,2019 was reviewed by An-Najah National University IRB committee and was approved on **26th Feb 2019.**

Hasan Fitian, MD
IRB Committee Chairman
An-Najah National University

IRB
IRB

Appendix (2)

استمارة بحث علمي

جامعة النجاح الوطنية

كلية الدراسات العليا

ماجستير علوم صيدلانية

استمارة رقم ( )

2019/2020

هذا الاستبيان تقوم به طالبة ماجستير علوم صيدلانية في جامعة النجاح الوطنية لغرض الدراسة العلمية لتقييم الفعالية والأعراض الجانبية الناتجة عن دواء الدهنيات روزوفاستاتين لدى المرضى في فلسطين.

نرجو الاجابة على جميع الأسئلة بدقة علما بأنها ستستخدم لأغراض البحث العلمي.

القسم الأول : معلومات عامة

- ✓ **العمر:** _____
- ✓ **الجنس:** ☐ ذكر ☐ أنثى
- ✓ **المستوى التعليمي:** ☐ أمي ☐ المرحلة الابتدائية/الإعدادية ☐ المرحلة الثانوي ☐ التعليم الجامع ☐ أعلى من ذلك
- ✓ **أين تعيش في فلسطين؟** ☐ مدينة ☐ قرية ☐ مخيم
- ✓ **الحالة الاجتماعية:** ☐ أعزب ☐ متزوج ☐ مطلق ☐ أرمل
- ✓ **الدخل الشهري للعائلة بالشيكل:** ☐ اقل من1000 ☐ 3000-1000 ☐ 5000-3000 أكثر من 5000
- ✓ **هل لديك تأمين صحي؟** ☐ نعم, تأمين حكومي ☐ نعم, تأمين خاص ☐ لا
- ✓ **الحالية الصحية بشكل عام:** ☐ ممتازة ☐ جيدة جدا ☐ جيدة ☐ مقبولة ☐ سيئة

القسم الثاني : التاريخ المرضي

سبب الحضور للطبيب :

الامراض التي تعاني منها :

هل تستعمل ادوية اخرى غير روزوفاستاتين : ☐لا ☐نعم

(في حال الجواب ب نعم) ما هي الادوية الاخرى :

No.	Medication

نسبة الكولسترول في الدم :

	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
قبل العلاج				
بعد العلاج 1				
بعد العلاج 2				
بعد العلاج 3				

جرعة الدواء : ☐ 20 mg ☐ 10 mg

الاسم التجاري:

مدة استعمال روزوفاستاتين : ☐ شهر ☐ شهرين ☐ ثلاث شهور ☐ أكثر

القسم الثالث : الأعراض الجانبية من الدواء

هل عانيت من اي من الاعراض التالية بعد استعمال دواء خفض الدهون:

الاعراض الجانبية	نعم	لا
الم في العضلات		
الم في المفاصل		
التهاب البلعوم		
الم في الراس		
غثيان		
تعب عام		
امساك		
دوخة		
الم في المعدة		
انفلونزا		
التهاب المسالك البولية		
تشنجات		
اكتئاب		
مشاكل في النوم		

جامعة النجاح الوطنية

كلية الدراسات العليا

"مراقبة روزوفاستاتين بعد التسويق في المختبر وعلى المرضى الفلسطينيين"

إعداد

نورس رضواني

إشراف

أ. د. عبد الناصر زيد

د. رواء الرمحي

قدمت هذه الاطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في الصيدلة السريرية في جامعة النجاح الوطنية نابلس- فلسطين.

2021

"مراقبة روزوفاستاتين بعد التسويق في المختبر وعلى المرضى الفلسطينيين"

إعداد

نورس رضواني

إشراف

أ. د. عبد الناصر زيد

د. رواء الرمحي

الملخص

المقدمة:

دواء روزوفاستاتين يستخدم للتقليل من نسبة الكوليستيرول الموجود في الدورة الدموية، الذي بدوره يؤدي لحدوث التجلطات وأمراض القلب والاوعية الدموية والتي تعتبر سبب رئيسي للوفاة. يتواجد دواء روزوفاستاتين في فلسطين بجرعتين 10 ملغم و20 ملغم.

الاهداف:

تهدف هذه الدراسة الى مقارنة الاصناف التجارية الموجودة في الصيدليات الفلسطينية من ناحية الفعالية الدوائية في تقليل نسبة الكوليسترول في الدم والاعراض الجانبية التي يسببها الدواء. بالاضافة الى المقارنة بين الاصناف الدوائية من ناحية احتواءها على المادة الفعالة.

الطريقة:

تم فحص الادوية والمقارنة بينها على مرحلتين، الاولى كانت في المختبر وتم من خلالها ملاحظة أي خلل في الخصائص الخارجية للحبوب الدوائية، على سبيل المثال اللون والشكل او وجود أي خلل في غلاف الحبة الدوائية. بالاضافة الى فحص وحساب نسبة المادة الفعالة الموجودة في الاصناف التجارية وكذلك سرعة ذوبان الحبة الدوائية التي تحتوي على روزوفاستاتين في بيئة شبيهة لجسم الانسان وذلك باستخدام برنامج لتحليل العينات. والمرحلة الثانية اشتملت على 94 مريض لديهم نسبة عالية من الكوليسترول في الدم ويستعملون احد الاصناف التجارية التي تحتوي على دواء روزوفاستاتين، تم الطلب منهم لتعبئة استبيان يحتوي على معلومات عن التاريخ المرضي

للمشاركين، ونسبة الكوليسترول عند البدء بتناول الدواء ومن ثم مراقبتهم من ناحية نزول الكوليسترول في الدم والاعراض الجانبية التي يسببها الدواء.

النتائج:

يتواجد في فلسطين اربع اصناف تجارية تحتوي على دواء روزوفاستاتين بجرعتين 10 ملغم و 20 ملغم. بالبداية من ناحية الخواص الخارجية المرئية للحبة، جميع الاصناف كانت بحالة جيدة ولا يوجد أي اثار غير طبيعية. اخذت الحبوب ما يقارب 2 – 3 دقائق للتفكك. بالاضافة الى ان نسبة وجود المادة الفعالة في الاصناف التجارية جميعها كانت ضمن النسبة المطلوب، حيث كانت النتائج تتراوح ما بين 90% – 110% لكلا الجرعتين 10 ملغم و 20 ملغم. وبالنسبة لفحص ذوبان حبوب دواء روزوفاستاتين عند وضعه في بيئة تحاكي جسم الانسان لمدة نصف ساعة كانت جميع النتائج مقبولة، وكانت النسب ما بين 85% – 115%.

في المرحلة الثانية من هذا البحث العلمي، تم اخذ الاذن من 94 مريض للمشاركة في تعبئة الاستبيان. كان معظم المشاركين من النساء بنسبة 55.3%. تراوحت الاعمار ما بين 27 – 83 سنة، 81.9% من المرضى كانوا يستعملون ادوية اخرى بالاضافة الى دواء روزوفاستاتين. بالنسبة للاعراض الجانبية, احتل الم العضلات النسبة الاعلى بين المرضى المشاركين بنسبة 51.1% ويليه الم الراس بنسبة 26.6%، بالاضافة الى عدد من الاعراض الجانبية شكى منها المرضى لكن بنسب اقل مثل الامساك والغثيان والم في الحلق. اوضحت هذه الدراسة العلاقة بين الجرعة الدوائية والاعراض الجانبية، حيث ان نسبة ظهور الاعراض الجانبية كانت اعلى عند المرضى الذين استعملوا الجرعة الاعلى 20 ملغم روزوفاستاتين.

الاستنتاج:

جميع الاصناف التجارية الموجودة في فلسطين التي تحتوي على دواء روزوفاستاتين لكلا الجرعتين 10 ملغم و 20 ملغم تجاوزت الفحوصات في المختبر وعلى المرضى من ناحية فعالية الدواء العلاجية والاعراض الجانبية التي يسببها الدواء.