https://doi.org/10.55453/rjmm.2024.127.5.5
The article was received on November 25, 2023, and accepted for publishing on February 5, 2024.

REVIEW

Immunomodulatory Effects of Statins in the Treatment and Prophylaxis of Influenza Viruses

Mojtaba Sharti[1], Hadi E.G. Ghaleh[2], Amir Vahedian-Azimi[3], Reza Ranjbar[4], Morteza Izadi[5], Ali Razei[1]

[1] Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran
[2] Applied Virology Research Center, Baqiyatallah University of Medical Science, Tehran, Iran
[3] Trauma Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[4] Molecular Biology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[5] Health Research Center, Life Style Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

Correspondence: Ali Razei, ali.razei@gmail.com

Abstract: *Background and aim: Influenza, commonly referred to as "the flu," is an infectious illness caused by influenza viruses (IV). Despite the availability of efficient antiviral drugs, the IV still significantly increases mortality. Antiviral drugs swiftly remove these viruses from pulmonary secretions, suggesting that a prolonged inflammatory response may be to blame for the poor result. Therefore, using immunomodulatory medications looks advantageous. Numerous anti-inflammatory effects are produced by statins. Numerous retrospective studies recommended that statins be considered for IV therapy. This study set out to comprehensively examine the immunomodulatory potential of statins in IV prophylaxis and therapy. Methods: From the beginning until 25 March 2022, a number of electronic databases (Scopus, EMBASE, PubMed, Web of Science, ProQuest, OVID, EBSCO, and CINAHL) were searched for cohort studies and randomized trials assessing the association between outcomes or risk of infections and statin therapy. Data were gathered on the investigated characteristics, measuring statin usage, quality evaluation, and results (set for potential confounders). Results: Finding additional therapeutic agents for influenza prevention and management is crucial since there are uncertain public health issues regarding the clinical efficacy of conventional medications. Pro-inflammatory cytokines are released as a result of influenza. According to the results, by using anti-inflammatory medications, severe influenza infections can be prevented along with pleiotropic effects. As a result, statins, which are cardioprotective medications with immunomodulatory and anti-inflammatory properties, may be beneficial for individuals with IV. Conclusion: Based on the positive immunomodulatory effects of statin administration, our systematic review's findings suggested that IVs may be prevented and treated.*

Keywords: *immunomodulation, antiviral, anti-inflammation, statin, prophylaxis, Influenza viruses*

INTRODUCTION

Despite the Influenza virus (IV) being recognized as a serious pathogen during the past century, influenza continues to cause a sizable number of ailments. According to estimates, only in the US in 2017–2018. (Table 1) [1].

Universally, The worldwide WHO estimates that each year, influenza epidemics cause 3,000,000–5,000,000 serious illnesses, with 290,000–650,000 recorded fatalities due to the severity of IV [2]. Although yearly influenza vaccinations are advised and antiviral drugs are available, both have a number of limitations. Following influenza infection, immunological dysregulation, which is determined to release the pro-inflammatory cytokines generating major risk factors for mortality and morbidity, is the cause of the severity of the disease and clinical presentations [3]. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are the most significant implicated cytokines, generating innate immune responses and inflammation [4]. The antigenic changes over time (requiring a precise strain match annually), vaccine strain egg-adapted changes, slow manufacturing processing, the absence of cross-reactivity, brief duration of protection, and poor immunogenicity in certain populations (for example, the elderly) all play a significant role in the effectiveness of the seasonal influenza vaccine [5,6]. If given at the right moment during the illness, antiviral medications such as neuraminidase inhibitors might have a profound effect; otherwise, they have

only a subtle impact on clinical symptoms [7]. Prophylaxis is defined as a preventative measure against disease.

A preventative measure has immediate effects against response-triggering and can reduce the systemic reaction to physiological stress or illness. This development might greatly reduce the detrimental disease-related circumstances [8]. The most often given medications in the world are statins, which decrease cholesterol. Statins block the enzyme 3-hydroxy-3-methyl glutaryl coenzyme-A reductase, which catalyzes the rate-restrictive step of cholesterol production. Statins have been shown to have positive cardiovascular benefits (Figure 2). [9].

Table 1: It was extremely well-established how viral respiratory tract illnesses compare epidemiologically

Disease	Flu	COVID-19	SARS	MERS
Disease Causing Pathogen	Influenza virus	SARS-CoV-2	SARS-CoV	MERS-CoV
R_0 Basic Reproductive Number	1.3	2.0 - 2.5 *	3	0.3 - 0.8
CFR Case Fatality Rate	0.05 - 0.1%	~3.4% *	9.6 - 11%	34.4%
Incubation Time	1 - 4 days	4 - 14 days *	2 - 7 days	6 days
Hospitalization Rate	2%	~19% *	Most cases	Most cases
Community Attack Rate	10 - 20%	30 - 40% *	10 - 60%	4 - 13%
Annual Infected (global)	~ 1 billion	N/A (ongoing)	8098 (in 2003)	420
Annual Infected (US)	10 - 45 million	N/A (ongoing)	8 (in 2003)	2 (in 2014)
Annual Deaths (US)	10,000 - 61,000	N/A (ongoing)	None	None

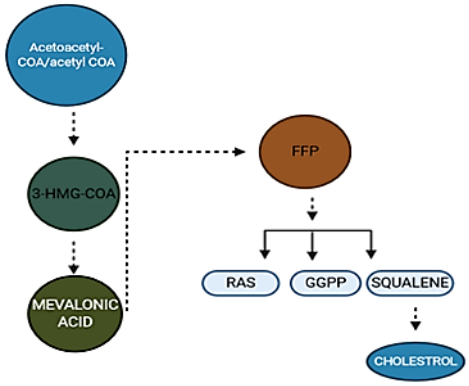

Figure 1: Statins' advantageous cardiovascular effects

Regardless of its effects on cholesterol levels, statins have been shown in clinical and experimental studies to decrease inflammation, improve endothelial function, and stabilize atherosclerotic plaques through a direct mechanism [10]. Statins can also alter cell shape, which is necessary for viral propagation [11]. Despite conflicting scientific findings, several retrospective observational analyses identified a link between statin use and decreased IV morbidity effects in people. However, these evaluations are constrained by the significant variation in medication delivery timing and duration across contributors or the participation of pneumonia morbidity in the absence of laboratory-approved IV infection [12]. A systematic review of statins' possible immunomodulatory properties in the treatment and prevention of IVs was the goal of this assessment.

METHODS

From the beginning until 25 March 2020, a number of electronic databases (Scopus, PubMed, EMBASE, Web of Science, ProQuest, OVID, EBSCO, and CINAHL) were searched for cohort studies and randomized trials exploring the connection between statin prescription and the result or risk of infections. Data on trial characteristics, statin consumption measurement, quality analysis, and outcomes were retrieved (set for potential confounders).

Influenza and the immune system

IVs are single-stranded RNAs that belong to the Orthomyxoviridae family and are divided into 4 categories based on their negative sense, segmented, and ssRNA genomes [12]. (classes of A, B, C, and D). In the meantime, many animal species might contract the influenza A virus (IAV) [13]. The IAV genome is almost 13,500 bases long and has 8 ribonucleoproteins (RNP) units, which together may encode at least 17 different proteins, including the recently identified

NS3, M42, PA-N155, and PA-N182 [14].

The genetic characteristics and molecular makeup of the neuraminidase (NA) and hemagglutinin (HA) proteins allow for further classification of IAVs. However, 9 NA and 16 HA subtypes were shown to be present in both human and animal bodies [15]. There have been reports linking many important IAV-encoded proteins to the host immune response and virus pathogenesis to the viral infection. According to research, changes in viral proteins' amino acid composition are linked to greater immune evasion and illness severity in humans and birds caused by IAVs [16]. In order for B cells to start producing neutralizing antibodies, HA contains epitopes. Therefore, the primary factors influencing recombination processes and viral mutation are the HA epitopes [17]. An innate immune response is the initial line of defense for the body against viral infection. IAV replicates itself by concentrating on respiratory tract epithelial cells. Understanding the innate immune systems defending these cells against IAV infection is crucial. Pathogen-associated molecular patterns (PAMPs), which are present in airway epithelial cells, are identified by receptors such Toll-like receptor (TLR) 3, melanoma differentiation-associated protein 5 (MDA5), and retinoic acid-inducible gene I (RIGI) [18]. Different autocrine signaling pathways can trigger the production of class 1 and 3 interferons (IFNs) and other cytokines instead of locating PAMP [19]. IFN lambda receptor 1 (IFNLR1-IL10R2) and IFN alpha/beta receptor (IFNAR1-IFNAR2), which are the receptors for class 1 and class 3 IFNs, respectively, can result in the paracrine response, which in turn activates a number of ISGs with antiviral activity and, as a result, induces the defensive activity of neighboring cells against viral infection [20]. The majority of adaptive immunity against IAV infection comes from B and T cells. T lymphocytes are mostly recognized as CD8+ and CD4+. In order to create cytokines and other powerful chemicals that can stop viral replication and kill virus-infected cells, CD8+ T cells are developed into cytotoxic T lymphocytes (CTLs). T cells are therefore essential to limit viral infection [21]. The naive CD8+ T cells are stimulated by the DCs to go from the lungs to the draining lymph nodes' T-cell zone during IAV infection, where they differentiate and multiply into CTLs [22]. Additionally, IL-12, IL-2, class 1 IFN-, and IFNs help to differentiate CD8+ T cells into CTLs [23]. It has also been demonstrated that IFN- increases T-cell proliferation during IV [24]. The workings of CTL have been extensively studied. The CTLs create cytotoxic granules that contain chemicals like granzymes and perforin while the virus targets the cells [25]. Additionally, CTLs can activate death receptors in IAV-infected cells by secreting cytokines including TNF, TRAIL, and FASL [26]. Following infection, lymphoid organs, blood, and the infection site are circulated with virus-specific DCs and CTLs [27]. The differentiation and activation process during the first infection increases the memory CTL cells' effectiveness and proficiency in secondary infection, and the memory CTL cells respond swiftly to subsequent IAV infection [28]. Although neutralizing antibodies are protected from subsequent infection with the same IAV serotype, CTLs are epitope-specific in conserved IAV proteins including NP, PA, and M1. As a result, the CTL response is heterosubtypic [29]. CD4+ T cells are a crucial subset of immune cells that are involved in adaptive immunity against IAV infection. In mouse models, CD4+ T lymphocytes may promote MHC type 2 expression in epithelial cells and target IAV-infected epithelial cells [20]. The CD40 ligand (CD40L) is notable among the several co-stimulatory ligands produced by CD4+ T cells that are important in antibody production and B cell activation [21]. TNF, IL-2, and IFN- are examples of antiviral cytokines generated by Th1 effector CD4+ T cells that activate alveolar macrophages [22]. IFN- and IL-2 released by Th1 cells control CD8+ T-cell differentiation to clear viral infection [23]. Additionally, CD4+ T cells can develop into killer, Th17, Th2, follicular helper, regulatory, and rarely Th2 cells [24]. Antigen-offering cells attach to MHC type II-related peptides produced from viruses, and Th2 cells produce IL-13 and IL-4 primarily to encourage B cell responses [25]. It was discovered that the control of cellular immunity against IAV infection includes the Treg and Th17 cells.

Immunopathogenesis of Influenza

The primary targets of IV for infection are respiratory epithelial cells, which are also amplified cytokines by the choreographers [26]. Following first exposure, the offspring viruses that have multiplied inside of these cells can spread to other cell types, including alveolar macrophages. The inflammatory reactions start when infected cells die through necrosis or apoptosis [27]; acute inflammation is thought to be the body's main defense mechanism against damaging stimuli. In order for leukocytes and plasma to reach the site of extra-vascular injury, blood flow must be increased. Acute inflammation is identified by an increase in local temperatures and discomfort [3]. Acute inflammation is indicated by the activation of pro-inflammatory chemokines or cytokines [28]. Inflammatory cell recruitment may happen as a result of these pro-inflammatory chemokines or cytokines. Then, there is extensive tissue damage, immune cell infiltration, and a gradual expression of antiviral, inflammatory, and apoptotic genes [29]. Both the repair of the damage and the regeneration processes begin at the same time. Most of the time, this repair technique can fully restore the function [30].

The formation of hyaline membranes, diffuse alveolar damage, fibrotic healing, and fibrin exudate (Figure 3), which are thought to be signs of severe capillary damage, persistent organ dysfunction, and immunopathologic injury, are among the more pathologically severe alterations found for severe

inflammation related to cytokine storm. Additionally, the release of strong inflammatory chemokines and cytokines into the bloodstream can result in systemic cytokine storms and multiple organ failure [32].

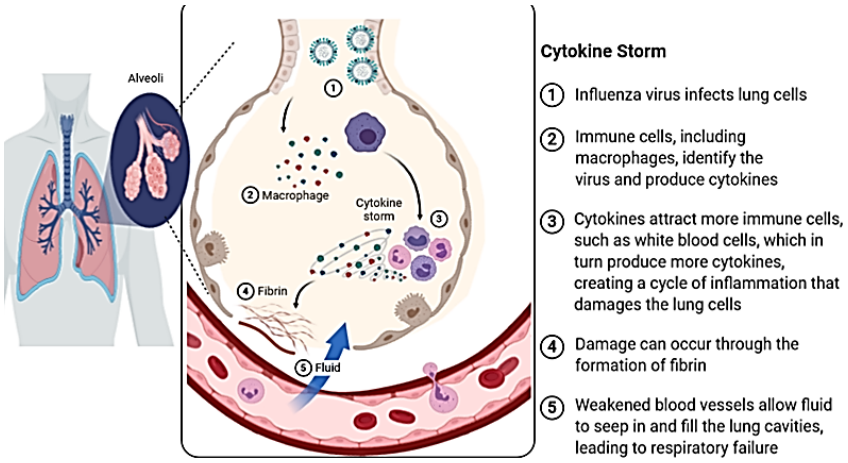

Figure 2: Severe inflammation related to cytokine storm

Because viral virulence and host resistance both have a role in the severity of influenza outcomes, it is imperative to use immunomodulatory treatment in addition to traditional antiviral medication. Indeed, several studies have shown that administering immunomodulatory medicines, with or without antiviral medications, can reduce organ damage and death from severe influenza. Additionally, the majority of these medications are not costly and are made simply, making them potentially useful in large-scale influenza pandemics. Here, the characteristics of statins and some instances of these were discussed.

Statins as immunomodulatory agents

The enzyme hydroxyl methylglutaryl-coenzyme A (HMG-CoA) reductase is inhibited by statins. By catalyzing the reduction of HMG-CoA for mevalonate during cholesterol synthesis, this enzyme can gauge the pace of the early step of the cholesterol biosynthesis pathway [33]. In addition to their ability to lower cholesterol levels, statins are pleiotropic cardioprotective medications that are gradually becoming recognized as direct cellular effect mediators. Statins inhibit downstream molecules, which are essential for viral contagiousness [34]. They reduce or prevent the production of downstream isoprenoid intermediates such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate (GGPP) (FPP). These isoprenoid intermediates interact with membranes when post-translational proteins are modified. Statins regulate GDP and GTP-bound states by controlling their isoprenylation and preventing them from switching from the cytosol to the membrane when they are inactive [35].

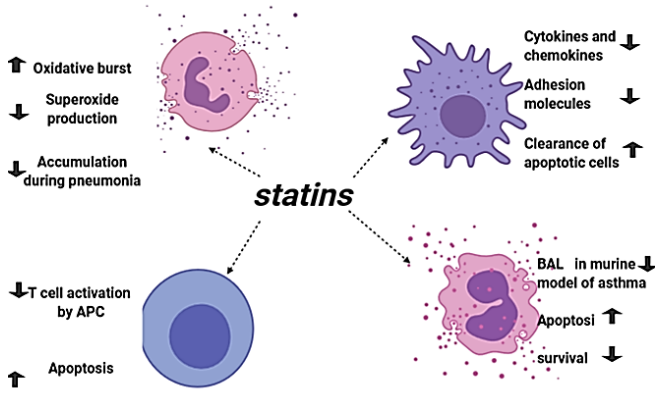

Figure 3: Some functions of statins

As a result, statins stop the activity and membrane translocation of isoprenoid intermediates and reduce their production. It is thought that lowering the isoprenylation of several proteins mediates the pleiotropic effects of statins.

This is best shown by the Rho GTPase family, which includes RhoA, Cdc42, and Rac, and which performs distinct roles dependent on the shape, secretion, motility, control, and proliferation of gene expression in cells [36]. To apply their activities and membrane interactions, members of the Ras family must add a farnesyl group to processes such as platelet activation, cell division, differentiation, intracellular vesicle transport, and the production of oxygen radicals [37]. These effects of statins include immunomodulatory actions such as the reduction of T-cell activation, the inhibition of inflammatory responses in neutrophils and macrophages, and the inhibition of a number of pro-inflammatory cytokines like TNF, IL6, and IL8. Furthermore, it has been demonstrated that blocking MAPK pathways such p38 MAPK, JNK, and ERK1/2 prevented the expression of RANKL, the production of cytokines and MMPs, and the degeneration of cartilage in different cells from RA patients (Figure 3). [38-42]

Use of immunomodulatory features of statins on IV treatment

According to three categories, including in vitro, human, and animal investigations, the effects of statin-related immune-modulation were examined to treat influenza in a number of studies. The following sections were used to review particular research from each category.

In vitro study

In the US Vaccine Effectiveness Network trial across 6 influenza courses (2011-2012 to 2016-2017), Havers et al. evaluated the influenza VE in statin users and nonusers with age higher than 45. All individuals with acute respiratory illnesses were screened for influenza at outpatient clinics. According to the data, out of 11692 eligible contributors, 3359 (30%) used statins, and 2806 (24%) tested positive for IV illness. Meanwhile, only 60% of nonusers and 78% of statin users obtained influenza vaccination. Setting for possible confounders came in at 39 percent (95 percent CI, 32 percent -45 percent) among nonusers and 22 percent (95 percent confidence interval [CI], 22 percent -47 percent) among statin users, with influenza VE coming in at 36 percent. They discovered no appreciable VE alteration as a result of statin use. Between nonusers and statin users, VE against influenza A(H3N2), A(H1N1) pdm09, and B viruses were comparable. When they analyzed the data by type and subtype, they discovered that the use of statin administration did not change the effect of vaccination on influenza [43].

According to research by Gower et al., lovastatin can stop virally induced cell-to-cell fusion and RSV replication. The experimental research showed that isoprenylation inhibition is a potential new antiviral strategy for treating or preventing severe RSV infection [44]. Statins, a widely used and affordable pharmacological medication, may be effective in preventing current and future influenza epidemics, particularly in less developed and underdeveloped nations, according to Mehrbod et al. By lowering cytokine over-expression and modulating strong inflammatory responses, statin therapy may protect the body from inflammatory reactions in the pulmonary system and other inflammatory reactions connected to severe influenza sickness. The availability of statins, which might be used as preventative or supplemental drugs to lessen the severity of the disease, and possible preventive medical therapy for unanticipated pandemics, may help to diminish the inflammatory repercussions of influenza that are connected with it [45]. Simvastatin and H1N1 elevated membrane localization and LC3 protein lipidation, according to Mehrbod et al. Simvastatin, however, has a direct influence on LC3 lipidation through a reduction in cholesterol, while H1N1's contribution to autophagy is more convoluted due to its effects on the activation of several autophagy-related genes to boost the autophagic flux. Their results were in line with those of an earlier study on the primary human lung mesenchymal cells, highlighting the relationship between the relative amount of LC3-II and the dynamic turnover of LC3-II through lysosome activity [46].

Animal study

Despite the ambiguous results, several animal studies showed that alternative statin medications may be protective against acute lung damage. In C57BL/6 mice infected by IAV, Haidari et al. observed that atorvastatin (40 mg/kg/day) prescription decreased the lung viral titers and mortality. Statins work directly against influenza by inhibiting the Rho/Rho-kinase pathway. The statins' protection against influenza might be viewed as a component of their cardiovascular event prevention benefits [47]. According to Lee et al., the treatment of simvastatin plus the neutralizing RANTES antibody effectively inhibited the growth of neutrophils caused by poly I:C in the lungs. Additionally, they said that simvastatin inhibits neutrophilia in poly I:C-induced pneumonia by inhibiting STAT3-mediated RANTES production. Understanding the etiology of viral pneumonia is crucial in order to develop effective anti-inflammatory or antiviral medications for certain inflammatory conditions. Simvastatin should be considered as a potential therapeutic option for viral pneumonia, particularly in neutrophilic inflammation due to a viral component, they further said. Simvastatin can reduce airway inflammation, but its exact mechanism of action has to be understood [48]. Simvastatin's efficacy against influenza A/PR/8/34 virus infection in the mouse model was evaluated by Glück et al. The first trial used oral administration of simvastatin. In a subsequent investigation, intraperitoneal administration was used to achieve high plasma levels. Bodyweight loss, survival

rate, histologic lung damage, and viral titers in the lungs and trachea were evaluated. Surprisingly, simvastatin treatment caused the mice to lose more body mass and have lower survival rates than the virus-infected control animals. Simvastatin also did not affect histological lesions, tracheas, or lung viral loads. In general, they demonstrated that simvastatin did not shield the mice from IV infection [49]. According to Radigan et al., rosuvastatin treatment did not successfully treat influenza A illness. Inflammation of the lungs, lung damage, and the degree of weight loss were comparable in rosuvastatin- and control-treated mice. Rosuvastatin treatment had no impact on mortality in influenza A-infected mice (A/WSN/33) Statins did not affect influenza A replication in vitro or its removal from the lung in vivo. Statins did not affect influenza A-related mortality and did not lessen the severity of the lung damage caused by the virus. According to them, there is no connection between HMG CoA reductase inhibitors and improved outcomes for patients with sepsis and pneumonia related to their effects on influenza A infection [50].

Human study

In critically ill patients with severe sepsis, Kruger et al. investigated the clinical and biochemical effects of atorvastatin treatment. Before using statins, the site stratified a phase II, prospective, multicenter, double-blind, randomized, and placebo-controlled experiment. A matching placebo or atorvastatin was given to 250 individuals in a cohort trial who had severe sepsis and acute infection (127 received placebos, 123 received statins) (20 mg daily). The results showed no interactions between treatment groups, showing that there were distinct behaviors across the groups throughout time (P = 0.26), and no variations in IL-6 concentrations (initial endpoint) between the placebo and atorvastatin groups (P = 0.76). The baseline IL-6 plasma titer was decreased (129 [87-191] vs. 244 [187-317] pg/ml; P = 0.01) in those who had previously taken statins. There was no difference between the two groups in terms of the length of hospital stays, hospital discharges at 28 or 90 days (15% vs. 19%), changes in Sequential Organ Failure Assessment scores, death at intensive care unit release, or negative effects. Patients on atorvastatin had reduced cholesterol (2.6 [0.06] vs. 2.4 [0.07] mmol/L; P = 0.006). Greater than 28-day mortality was detected for those randomly assigned to the placebo (28 percent vs. 5 percent; P = 0.01) than for those getting atorvastatin in the selected group of 77 past statin users. At 90 days, there were no statistically significant differences (11 percent vs. 28 percent; P = 0.06). A therapy with atorvastatin for severe sepsis did not appear to have an impact on IL-6 levels. A lower baseline IL-6 concentration in this population was associated with improved survival, while prior statin usage was associated with the continuation of atorvastatin [51].

According to Papazian et al., simvastatin (60 mg) prescriptions for supplementary VAP therapy did not lower day-28 mortality. Simvastatin did not substantially worsen any side effects. Although the superiority of a placebo to simvastatin was not tested in our investigation, it is important to note that day-28 mortality in the simvastatin group increased by approximately 6% absolute and by almost 8% absolute in the statin-naive category. It would be pertinent to look at the potential supremacy of a placebo over a statin as normal practice does not involve de novo statin administration in ICU patients with infection. They thus investigated the claim that simvastatin is preferable to a placebo. The results did not support the use of supplementary statin medication in ICU patients with VAP. Therefore, this result may be extended to ICU patients who have any type of nosocomial infection [52].

With the aid of connected administrative databases, Kwong et al. conducted a population-based cohort analysis across 10 influenza seasons (1996–2006) in Ontario, Canada. Before the start of the influenza season, they identified all persons over the age of 65 who had had an influenza vaccination, and they also separated those who had received prescription statins (23 percent) from those who had not (77 percent). A final cohort of 2,240,638 patients—exactly half of those taking statins—was obtained by matching based on propensity, which took into consideration each patient's likelihood of receiving a statin. Statins had poor protective effects against pneumonia hospitalization (odds ratio [OR] 0.92; 95 percent confidence interval [CI] 0.89-0.95), all-cause mortality (0.87; 95 percent CI 0.84-0.89), and pneumonia mortality within 30 days (0.84; 95 percent CI 0.77-0.91). The significantly decreased with time, varied between risk groups and propensity score quintiles, and remained unaltered across post-influenza season periods after multivariate regulation and while omitting multiple clarifications for each individual. They suggested that statin use could have a statistically significant, but little, protective effect on influenza morbidity, which was merely attributable to public health authorities and residual confounding. Additionally, doctors must focus on minimizing mortality and morbidity from the ensuing influenza epidemic [53].

CONCLUSIONS

The immunomodulatory effects of statins are mediated by a number of mechanisms, including direct activation of heme oxygenase and inhibition of major histocompatibility type II complexes, which interfere with the interaction between leukocytes and endothelium. The most crucial mechanism is intracellular inflammatory signaling, however. GTP-binding proteins serve as molecular on/off switches for various protein kinases, which makes them essential for intracellular

inflammatory signaling. Both the cycle's inactive and active stages require isoprenylation for the route to be activated. By blocking 3-hydroxy-3-methylglutaryl-CoA reductase, statins lessen but do not completely abolish protein isoprenylation. The response strength of the impacted signaling pathway is decreased by this drop in prenylated protein concentration. As a result, it could balance out the "cytokine storm" associated with IVs. Based on the aforementioned effects, statins were found to have direct antiviral effects in some cases when used at physiologically appropriate concentrations. This suggests that they may prove to be an effective adjuvant treatment in the fight against pandemic and seasonal influenza, particularly in health systems that cannot afford expensive vaccines or antiviral medications. Despite conflicting results from several research, statins are affordable and easily available medicines in underdeveloped nations. By controlling immune system cytokine overexpression and modulating severe inflammatory reactions, they may be used as preventative medication or therapy for influenza sickness.

Acknowledgments

The authors would like to thank the Clinical Development Unit of Baqiyatallah Hospital, Tehran, Iran, for guidance and advice.

Conflict of interest

The authors have no competing interests to declare that are relevant to the content of this article.

References:

1. Leonard AS, McClain MT, Smith GJ, Wentworth DE, Halpin RA, Lin X, Ransier A, Stockwell TB, Das SR, Gilbert AS, Lambkin-Williams R. The effective rate of influenza reassortment is limited during human infection. PLoS pathogens. 2017 Feb 7;13(2):e1006203.

2. Sherman AC, Mehta A, Dickert NW, Anderson EJ, Rouphael N. The future of flu: a review of the human challenge model and systems biology for advancement of influenza vaccinology. Front cell infect. 2019 Apr 17;9:107.

3. Ramos I, Fernandez-Sesma A. Modulating the innate immune response to influenza A virus: potential therapeutic use of anti-inflammatory drugs. Front Immunol. 2015 Jul 20;6:361.

4. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci. 2019 Jan;20(23):6008.

5. Harding AT, Heaton NS. Efforts to improve the seasonal influenza vaccine. Vaccines. 2018 Jun;6(2):19.

6. Nachbagauer R, Krammer F. Universal influenza virus vaccines and therapeutic antibodies. Clin. Microbiol. Infect. 2017 Apr 1;23(4):222-8.

7. Principi N, Camilloni B, Alunno A, Polinori I, Argentiero A, Esposito S. Drugs for influenza treatment: is there significant news?. Front Med (Lausanne). 2019 May 28;6:109.

8. Stults-Kolehmainen MA, Sinha R. The effects of stress on physical activity and exercise. Sports Med. 2014 Jan;44(1):81-121.

9. Fracassi A, Marangoni M, Rosso P, Pallottini V, Fioramonti M, Siteni S, Segatto M. Statins and the brain: more than lipid lowering agents?. Current neuropharmacology. 2019 Jan 1;17(1):59-83.

10. S Antonopoulos A, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. Curr Pharm Des. 2012 Apr 1;18(11):1519-30.

11. Shrivastava-Ranjan P, Flint M, Bergeron É, McElroy AK, Chatterjee P, Albariño CG, Nichol ST, Spiropoulou CF. Statins suppress Ebola virus infectivity by interfering with glycoprotein processing. MBio. 2018 May 1;9(3):e00660-18.

12. Vandermeer ML, Thomas AR, Kamimoto L, Reingold A, Gershman K, Meek J, Farley MM, Ryan P, Lynfield R, Baumbach J, Schaffner W. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study J Infect Dis. 2012 Jan 1;205(1):13-9.

13. Mostafa A, Abdelwhab EM, Mettenleiter TC, Pleschka S. Zoonotic potential of influenza A viruses: a comprehensive overview. Viruses. 2018 Sep;10(9):497.

14. Nogales A, Martínez-Sobrido L. Reverse genetics approaches for the development of influenza vaccines. J Mol Sci. 2017 Jan;18(1):20.

15. Du R, Cui Q, Rong L. Competitive cooperation of hemagglutinin and neuraminidase during influenza A virus entry. Viruses. 2019 May;11(5):458.

16. Hu J, Ma C, Liu X. PA-X: a key regulator of influenza A virus pathogenicity and host immune responses. Med Microbiol Immunol. 2018 Nov;207(5):255-69.

17. Lee CC, Yang CY, Lin LL, Ko TP, Chang AH, Chang SS, Wang AH. An effective neutralizing antibody against influenza virus H1N1 from human B cells. Sci Rep. 2019 Mar 14;9(1):1-1.

18. . Biondo C, Lentini G, Beninati C, Teti G. The dual role of innate immunity during influenza. Biomed. J. 2019 Feb 1;42(1):8-18.

19. Musella M, Manic G, De Maria R, Vitale I, Sistigu A. Type-I-interferons in infection and cancer: Unanticipated dynamics with therapeutic implications. Oncoimmunology. 2017 May 4;6(5): e1314424.

20. Stanifer ML, Pervolaraki K, Boulant S. Differential regulation of type I and type III interferon signaling. Int J Mol Sci. 2019 Jan;20(6):1445.

21. Hufford MM, Kim TS, Sun J, Braciale TJ. The effector T cell response to influenza infection. Influenza Pathogenesis and Control-Volume II. 2015:423-55.

22. Turner DL, Bickham KL, Farber DL, Lefrançois L. Splenic priming of virus-specific CD8 T cells following influenza virus infection. J Virol. 2013 Apr 15;87(8):4496-506.

23. Mitchell DM, Ravkov EV, Williams MA. Distinct roles for IL-2 and IL-15 in the differentiation and survival of CD8+ effector and memory T cells. J. Immunol. 2010 Jun 15;184(12):6719-30.

24. Mitchell DM, Ravkov EV, Williams MA. Distinct roles for IL-2 and IL-15 in the differentiation and survival of CD8+ effector and memory T cells. Front Immunol. 2010 Jun 15;184(12):6719-30.

25. Osińska I, Popko K, Demkow U. Perforin: an important player in immune response. Cent Eur J Immunol. 2014;39(1):109.

26. Zhou X, Jiang W, Liu Z, Liu S, Liang X. Virus infection and death receptor-mediated apoptosis. Viruses. 2017 Nov;9(11):316.

27. Kang SS, Herz J, Kim JV, Nayak D, Stewart-Hutchinson P, Dustin ML, McGavern DB. Migration of cytotoxic lymphocytes in cell cycle permits

local MHC I–dependent control of division at sites of viral infection. J Exp Med. 2011 Apr 11;208(4):747-59.

28. Muraro E, Merlo A, Martorelli D, Cangemi M, Dalla Santa S, Dolcetti R, Rosato A. Fighting viral infections and virus-driven tumors with cytotoxic CD4+ T cells. Front Immunol. 2017 Feb 27;8:197.

29. van de Sandt CE, Pronk MR, van Baalen CA, Fouchier RA, Rimmelzwaan GF. Variation at extra-epitopic amino acid residues influences suppression of influenza virus replication by M158-66 epitope-specific CD8+ T lymphocytes. J Virol. 2018 Jun 1;92(11): e00232-18.

30. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. Science translational medicine. 2014 Dec 3;6(265):265sr6-.

31. Tomashefski Jr JF. Pulmonary pathology of acute respiratory distress syndrome. Clinics in chest medicine. 2000 Sep 1;21(3):435-66.

32. Liu Q, Zhou YH, Yang ZQ. The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell Mol Immunol. 2016 Jan;13(1):3-10.

33. Burg JS, Espenshade PJ. Regulation of HMG-CoA reductase in mammals and yeast. Prog Lipid Res. 2011 Oct 1;50(4):403-10.

34. Liao JK, Laufs U. Pleiotropic effects of statins. Annu. Rev. Pharmacol. Toxicol.. 2005 Feb 10;45:89-118.

35. Waller DD, Park J, Tsantrizos YS. Inhibition of farnesyl pyrophosphate (FPP) and/or geranylgeranyl pyrophosphate (GGPP) biosynthesis and its implication in the treatment of cancers. Crit Rev Biochem Mol Biol. 2019 Jan 2;54(1):41-60.

36. Mehrbod P, Omar AR, Hair-Bejo M, Haghani A, Ideris A. Mechanisms of action and efficacy of statins against influenza. Bio Med Res Iint. 2014 Oct;2014.

37. Jaśkiewicz A, Pająk B, Orzechowski A. The many faces of Rap1 GTPase. Int J Mol Sci. 2018 Oct;19(10):2848.

38. Dinarello CA. Anti-inflammatory agents: present and future. Cell. 2010 Mar 19;140(6):935-50.

39. Lim MX, Png CW, Tay CY, Teo JD, Jiao H, Lehming N, Tan KS, Zhang Y. Differential regulation of proinflammatory cytokine expression by mitogen-activated protein kinases in macrophages in response to intestinal parasite infection. Infect Immun. 2014 Nov;82(11):4789-801.

40. Rezaie-Majd A, Maca T, Bucek RA, Valent P, Müller MR, Husslein P, Kashanipour A, Minar E, Baghestanian M. Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. Arteriosclerosis, thrombosis, and vascular biology. 2002 Jul 1;22(7):1194-9.

41. Ramos I, Fernandez-Sesma A. Modulating the innate immune response to influenza A virus: potential therapeutic use of anti-inflammatory drugs. Frontiers in immunology. 2015 Jul 20;6:361.

42. Yang Y, Kim SC, Yu T, Yi YS, Rhee MH, Sung GH, Yoo BC, Cho JY. Functional roles of p38 mitogen-activated protein kinase in macrophage-mediated inflammatory responses. Med Inf. 2014 Oct;2014.

43. Havers FP, Chung JR, Belongia EA, McLean HQ, Gaglani M, Murthy K, Zimmerman RK, Nowalk MP, Jackson ML, Jackson LA, Monto AS. Influenza vaccine effectiveness and statin use among adults in the United States, 2011–2017. Clin Infect Dis. 2019 May 2;68(10):1616-22.

44. Gower TL, Graham BS. Antiviral activity of lovastatin against respiratory syncytial virus in vivo and in vitro. Antimicrobial agents and chemotherapy. 2001 Apr 1;45(4):1231-7.

45. Mehrbod P, Omar AR, Hair-Bejo M, Haghani A, Ideris A. Mechanisms of action and efficacy of statins against influenza. Biomed Res Int. 2014 Oct;2014.

46. Mehrbod P, Hair-Bejo M, Tengku Ibrahim TA, Omar AR, El Zowalaty M, Ajdari Z, Ideris A. Simvastatin modulates cellular components in influenza A virus-infected cells. Int J Mol Med. 2014 Jul 1;34(1):61-73.

47. Haidari M, Ali M, Casscells SW, Madjid M. Statins block influenza infection by down-regulating Rho/Rho kinase pathway.

48. Lee CS, Yi EH, Lee JK, Won C, Lee YJ, Shin MK, Yang YM, Chung MH, Lee JW, Sung SH, Ye SK. Simvastatin suppresses RANTES-mediated neutrophilia in polyinosinic–polycytidylic acid-induced pneumonia. European Respiratory Journal. 2013 May 1;41(5):1147-56.

49. Glück B, Schmidtke M, Walther M, Meerbach A, Wutzler P. Simvastatin treatment showed no prophylactic effect in influenza virus-infected mice. J Med Virol. 2013 Nov;85(11):1978-82.

50. Radigan KA, Urich D, Misharin AV, Chiarella SE, Soberanes S, Gonzalez A, Perlman H, Wunderink RG, Budinger GS, Mutlu GM. The effect of rosuvastatin in a murine model of influenza A infection. PloS one. 2012 Apr 20;7(4):e35788.

51. Kruger P, Bailey M, Bellomo R, Cooper DJ, Harward M, Higgins A, Howe B, Jones D, Joyce C, Kostner K, McNeil J. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med. 2013 1;187(7):743-50.

52. Papazian L, Roch A, Charles PE, Penot-Ragon C, Perrin G, Roulier P, Goutorbe P, Lefrant JY, Wiramus S, Jung B, Perbet S. Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: a randomized clinical trial. Jama. 2013 Oct 23;310(16):1692-700.

53. Kwong JC, Stukel TA, Lim J, McGeer AJ, Upshur RE, Johansen H, Sambell C, Thompson WW, Thiruchelvam D, Marra F, Svenson LW. The effect of universal influenza immunization on mortality and health care use. PLOS Med. 2008 Oct; 5(10): e211.