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ORIGINAL ARTICLE

Herpes zoster infection and statins: which implications in clinical practice?

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Abstract

Herpes zoster (HZ), which is caused by reactivation of latent varicella zoster virus (VZV), constitutes a major public health concern in both short- and long-term periods. Over the last years, several epidemiological studies have demonstrated that statin use is associated with increased risk of HZ at cerebral level. Because statins are among the most popular and best-selling drugs in western countries, this potential negative pleiotropic effect could have important implications in the daily clinical practice. In the present manuscript, we reviewed the available data on the statin use and the relative risk of HZ infection.

Keywords Herpes zoster · Statin · Immunomodulatory effect

Introduction

Herpes zoster (HZ), which is caused by reactivation of latent varicella zoster virus (VZV), constitutes a major public health concern in both short- and long-term periods [1–3]. Recent epidemiological analyses have demonstrated that both the incidence and the severity of HZ, as well as its debilitating sequelae, such as post-herpetic neuralgia (PHN), increase with age [4]. Intriguingly, over the last years, a growing body of evidences and analyses have reported that statin use is associated with increased risk of HZ [5–9]. Statins are among the most popular and best-selling drugs in western countries over the last two decades [10]. They play a pivotal role in both primary and secondary prevention of cardiovascular disease (CVD) [11, 12]; moreover, several investigations have demonstrated systemic anti-inflammatory and immunomodulating properties of statins, suggesting their potential benefit besides their lipid-lowering effects [13]. However, like every drug, also statins have some side effects, as lowering the immune system, allowing the potential reactivation of latent infections. Considering that both the lifetime risk of HZ and the statin prescription increase with age, this potential pleiotropic "side effect" of statins should be carefully considered in clinical practice, especially in patients with comorbidities which are associated, per se, with an increased risk of HZ, i.e. rheumatoid arthritis (RA), inflammatory bowel disease (IBD), chronic obstructive pulmonary disorders (COPD), depression, chronic kidney disease (CKD), in those with diabetes (DM) and/or immunocompromising conditions, as well as in frail elderly patients [14]. Several studies have analysed the relationship between statin exposure and HZ risk over the last 4 years and this association could have important clinical implications in different areas of medicine. Therefore, we have reviewed the current available data on this issue.

Pleiotropic effects of statins

Statins, as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), are lipid-lowering agents (Fig. 1) used for both primary and secondary prevention of atherosclerotic CVD. Moreover, these drugs show some cholesterol-

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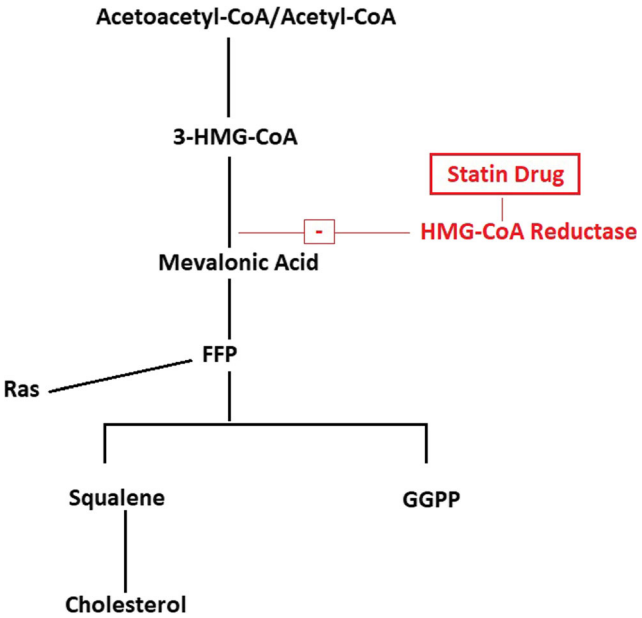

Fig. 1 Mechanism of action of statins. 3-HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; GGPP, geranylgeranylpyrophosphate; FFP, farnesylpyrophosphate

independent or "pleiotropic" effects on the endothelial function in addition to anti-inflammatory, anti-thrombotic and immunomodulatory effects [15]. More recently, an increasing number of investigations have demonstrated that the pre-treatment by and regular administration of statins may result in a beneficial effect in preventing and/or treating infectious diseases [16, 17]. Furthermore, their anti-inflammatory and immunomodulatory effects seem to be able to reduce the risk of mortality due to different viral infections [18, 19]. However, other recent epidemiological findings reported that the protecting effects of statins in infectious disease should not be extended to HZ infection [5–9].

Search strategy

We conducted a review of the PubMed database up to July 2018. The relevant studies, in English language, were identified through search engine using a combined text words and MeSH (Medical Subject Headings) search strategy. The following combination of keywords was used: "Herpes Zoster and statins"; "Zoster and statins"; "Herpes zoster, statins and elderly" and "Herpes Zoster and drugs". Moreover, we searched the bibliographies of target studies for additional references.

Current evidences from the literature: general overview

The treatment of patients with HZ both in the acute phase and during the long-term period is well established. However, this potential novel adverse relationship between statins and HZ might complicate the treatment, especially in patients with cardiovascular comorbidities. The analysis of the current medical literature revealed five large studies on this matter [5–9], conducted between 2014 and 2018. These investigations, which enrolled patients in different countries, demonstrated a mildly higher risk of HZ in statin users and recommended in some cases the use of a zoster vaccine in patients who received statin therapy. In these investigations, the absence of common inclusion criteria, treatment modalities and co-morbidities has led to intriguing but provisional results. Moreover, the lack of a consensus opinion on this matter does not allow conclusive and unequivocal approaches in these patients, leaving the choice of the most appropriate treatment strategy in a "grey zone". Indeed, in the current recommendations for the treatment of HZ, the potential negative pleiotropic effects of statins are not considered, even though, as additional confounder, an increased risk of acute cardiovascular events (i.e. stroke and acute myocardial infarction) has been reported in zoster patients [20, 21].

The main findings of the clinical studies on the risk of HZ infection in statin users are shown in Table 1. Among the five investigations, three enrolled patients aged > 18 years old [5, 7, 8], while one included subjects aged > 20 years old [6] and one focused the analysis only in elderly patients aged ≥ 66 years old [9]. Three studies were performed in Asia [6–8] while two in western countries [5, 9]. All the studies considered different comorbidities, ranging from systemic lupus erythematosus (SLE), IBD, COPD, DM, depression, cancer, HIV infection, RA and CKD. Conversely, four out of the five studies [5–7, 9] described the baseline presence of CVD and of the related risk factors (Table 2). The same studies assessed also diabetes as comorbidity, but only one [9] reported a specific sub-analysis on the risk of HZ infection in diabetic patients treated with statins. The type of statin administered during the follow-up period was collected in two studies but only Chen et al. [6] assessed the hazard ratio (HR) of HZ associated with the annual average of the defined daily dose (DDD) of the individual statin. The follow-up period of the studies ranged from 5 to 13 years.

Statins and risk of herpes zoster

All the studies reported an increased risk of HZ infection in statin users (Table 1). Kim et al., performing a propensity score-matched analysis on a large population, observed that, overall, statins significantly increase the risk of HZ infection by 25% (HR 1.2, 95% CI 1.15–1.37, $p < 0.0001$). Moreover, the risk resulted greater (39%) in patients aged 70 or older (HR 1.39, 95% CI 1.12–1.73, $p = 0.003$). By contrast, no significant differences in the risk of HZ infection were detected in patients younger than 60 years old [7]. Similar findings were

Table 1 Clinical studies on the risk of HZ infection in statin users

Author	Year	Population	No. of pts	Age (enrolment)	Design	Follow-up (years)	Outcome	Main findings
Kim et al. [7]	2018	South Korea	▪ 25,726 statin users ▪ 25,726 non-statin users [matched 1:1 according to a propensity score]	> 18	Propensity score-matched analysis	11	Development of HZ over 11 years	● Statin users had a significantly higher risk of HZ (HR 1.2, 95% CI 1.15–1.37, $p < 0.0001$) ● Higher risk in pts aged > 70 years old (HR 1.39, 95% CI 1.12–1.73, $p = 0.003$) ● Significant cumulative dose effect between the risk of HZ and the duration of statin exposure ($p < 0.0001$)
Matthews et al. [5]	2016	UK	▪ 144,959 pts with HZ ▪ 549,336 control pts	> 18	Matched case-control study	11	Quantify the effect of exposure of statins on the risk of HZ	● Statin exposure was associated with a mild increase in risk of HZ (OR 1.13, 95% CI 1.11–1.15) ● Dose-responder relationship between statins and HZ ● Attenuation of the excess risk over time among pts who had stopped statin therapy
Chen et al. [6]	2015	Taiwan	▪ 53,069 pts with statin therapy for at least 3 months ▪ 53,069 pts without statin therapy [matched 1:1 according to a propensity score]	> 20	Propensity score-matched analysis	5	HZ infection rate	● Pts in the statin cohort had a 21% higher risk of contracting HZ [95% CI 1.13–1.29] ● Higher risk in women ● The incidence of HZ infection increased with age and CCI in both cohorts ● A higher DDD was associated with a significantly increased risk of HZ ● Younger statin users are at higher risk of HZ infection (< 49 years, HR 1.35, $p < 0.01$)
Chung et al. [8]	2014	Taiwan	▪ 47,359 pts with HZ ▪ 142,077 controls	> 18	Population-based controlled study	10	To assess the relationship between HZ and previous statin prescription	● Statin users had a higher risk of HZ compared to non-statin users (OR 1.29, 95% CI 1.25–1.34, $p < 0.001$) ● Younger statin users were at higher risk of HZ
Antoniou T et al. [9]	2014	Canada	● 494,651 statin users ● 494,651 statin non-users	≥ 66	Population-based retrospective study	13	- New diagnosis of HZ - To compare the risk of HZ among statin and non-statin users	● Statin-treated pts were at increased risk of developing HZ (HR 1.35, 95% CI 1.10–1.17) ● Statin users with concomitant DM had a higher risk of HZ infection (HR 1.18, 95% CI 1.09–1.27)

Pts, patients; *HZ*, herpes zoster; *HR*, hazard ratio; *OR*, odds ratio; *CI*, confidence interval; *DM*, diabetes mellitus

Table 2 Cardiovascular risk factors, diabetes mellitus and type of statin evaluated in the studies on the relationship between the risk of HZ and statin use

Author	CVD investigated	Diabetes	Type of statin evaluation
Kim et al. [7]	AMI; TIA; HF; AF; PAD; carotid stenosis; VHD	Yes	No
Matthews et al. [5]	CVD [subtype not specified]	Yes	No
Chen et al. [6]	HT; stroke	Yes	Yes [simvastatin; lovastatin; pravastatin; fluvastatin; atorvastatin; rosuvastain]
Chung et al. [8]	NR	NR	No
Antoniou T et al. [9]	AMI; angina; HT; stroke; CABG	Yes [specific sub-analysis on the risk of HZ infection in diabetic statin users]	Yes [atorvastatin; cerivastatin; fluvastatin; lovastatin; pravastatin; rosuvastatin; simvastatin]

AMI, acute myocardial infarction; *HF*, heart failure; *AF*, atrial fibrillation; *PAD*, peripheral artery disease; *VHD*, valvular heart disease; *CVD*, cardiovascular disease; *HT*, arterial hypertension; *CABG*, coronary artery by-pass grafting; *NR*, not reported; *HZ*, herpes zoster

described by Matthews et al. who demonstrated a mild, but significant, increase in risk of HZ (OR 1.13, 95% CI 1.11–1.15) after statin exposure [5]. On the other hand, Chen et al., after a follow-up period of about 5 years, reported that patients treated with statins had a 21% higher risk of contracting HZ infection when compared to non-statin receivers. Furthermore, the risk of infection was higher for women (HR 1.31, 95% CI 1.20–1.43) and increased with increasing Charlson Comorbidity Index (CCI) [6]. Similarly, Chung et al. reported that statin users had a higher risk of HZ infection compared to non-statin users (OR 1.29, 95% CI 1.25–1.34, $p < 0.001$) [8] and Antoniu et al., by conducting a population-based retrospective study on individuals living in Ontario, confirmed that patients treated with statins had a higher risk of HZ infection (HR 1.35, 95% CI 1.10–1.17) [9]. Altogether, the available data show that statin-treated patients, in the long-term period, have a mildly, but significantly, higher risk of HZ infection. In other words, despite the retrospective nature of some investigations and/or the identification of the sample population through a propensity score-matched analysis or the enrolment limited to elderly patients in other studies, all of them suggest an adverse effect of statins on the risk of HZ infection in the long-term period. In addition, although specific sub-analyses on the type of administered statin were not run in all the investigations, the results seem to indicate that the risk was not related to the specific statin molecule but to a generic immunomodulatory effect induced by the drug.

Age, statins and herpes zoster

From an epidemiological point of view, it is well established that the incidence of HZ infection increases with age [4]. However, some of the cited investigations intriguingly found that statin therapy somehow modifies the relationship between risk of HZ infection and age. For example, Chen et al. reported that younger statin users, aged < 49 years old, were at higher risk of HZ, while the risk of infection decreased with increasing age [6]. Similarly, Chug et al. found that younger statin users, defined as those aged between 18 and 44 years old, were at higher risk of suffering HZ than their older counterparts (OR 1.69, 95% CI 1.45–1.92) [8]. On the contrary, Matthews et al. observed that statins did not modify the relationship age risk of HZ ($p = 0.41$) [5]. An explanation of this phenomenon involving young patients has not been systematically proposed in the studies and it has been suggested a larger statin prescription in younger patients because of more lipid-rich diet [6] or that the effect of statins on HZ may be diluted in the elderly [5]. To this regard, further prospective investigations are strongly desirable, since statins are often prescribed in younger patients, as primary or secondary cardiovascular prevention. If statin/HZ risk association was confirmed in such studies, adequate prevention with a zoster vaccine should be considered as recommended procedure in these patients.

Duration of statin therapy, statin dose and risk of herpes zoster

Kim et al. reported that the risk of HZ is a function of duration of statin therapy [7]. Specifically, the risk of infection increased with length of statin exposure and this result remained unchanged after adjustment for age and gender ($p < 0.0001$). By contrast, Matthews et al. observed no clear evidences that the length of statin use modified the effect of the drug on the risk of HZ. However, they demonstrated that both current and recent (i.e. those with a last prescription during the 12 months preceding the infection) statin users showed an increasing trend in HZ risk according to the dose of statin (ORadj 1.27, 95% CI 1.15–1.41 and ORadj 1.35, 95% CI 0.91–2.01, respectively, $p < 0.001$ for trend in both groups) [5]. Similarly, Chen et al. observed that the annual average of the DDD of each type of statin was directly and significantly associated

with the increased risk of [6], confirming a dose-effect phenomenon, although the relationship between the duration of statin use and the risk of HZ needs to be further clarified.

Are diabetic patients treated with statins at higher risk of zoster infection?

Dyslipidaemia is common in diabetes. Several previous investigations have demonstrated that cholesterol-lowering treatment leads to a significant improvement in cardiovascular outcomes even in diabetic subjects with apparently unremarkable lipid profile [22, 23]. Moreover, the risk for a first cardiovascular event, such as acute myocardial infarction (AMI), in patients with diabetes is as high as the risk for a new AMI in non-diabetic patients with a prior event [24]. Therefore, the American National Cholesterol Education Program (NCEP) clinical guidelines have defined diabetes as a coronary heart disease (CHD) risk equivalent with similar intensity and goal of cholesterol-lowering therapy [25]. Nowadays, risk-reducing statin therapy is recommended for nearly all patients with diabetes aged 40 or older, regardless of their cholesterol level. However, considering the potential higher relative risk of HZ infection in young and middle-age patients receiving statins and that type II diabetes, per se, has been associated with an increased risk of HZ, careful monitoring of these subgroups of patients in the long-term period could be advisable. Indeed, Antoniou et al. observed that, in the subgroup of patients with DM, statin users had higher risk of HZ infection compared to non-statin users (HR 1.18, 95% CI 1.09–1.27) [9]. These findings have important implications in the management of these patients, since most diabetic patients are dyslipidaemic and/or assume statin, and consequently are at risk of developing HZ. Because of the indubitable benefit of statins in term of severe cardiovascular adverse events in diabetic patients, the administration of HZ vaccine should probably be considered in these subjects.

Unsolved questions

Over the last 4 years, several epidemiological studies have reported that statin use is associated with increased risk of HZ [5–9], despite many confounding factors, such as comorbidities, age and medications (Fig. 2). Over the last years, several cost-effective analyses on the use of statins have been performed. However, as more statin drugs become generic, patients at low risk for CVD may be treated cost-effectively. It also true that the potential interaction between statins and HZ may have not only potential clinical but also cost-benefit implications. As said before, the moderate higher risk of HZ among statin users has important implication for daily clinical practice and public health. Statins are among the most widely prescribed drugs in western countries, especially in middle-age and elderly patients, who are, per se, at risk of HZ. Antoniou et al. have estimated that about 20,000 cases of HZ, out of 628,000 episodes of HZ each year, could be attributable to the use of statins in American subjects aged 50 or older [9]. Therefore, adequate strategies for the prevention and treatment of HZ are mandatory to reduce the burden of the disease and its related costs, both in the acute phase and in the long-term period, especially in patients with PHN. In the cited studies, as well as in current literature, the full pathophysiological mechanisms by which statins increase the risk of HZ, as well as the potential antigenic targets, have not yet been established. However, several potential immunomodulatory effects have been proposed, as overviewed in Table 3. Statins decrease the synthesis of isoprenoid phosphates, which is required for the activation of Ras GTPases, causing, therefore, the impairment of T cell activation [26, 27]. In addition, by increasing the number of $CD4^{+}CD25^{+}$ T cells [28], by promoting the Th2-cell differentiation (which implies the suppression of Th1-type immune responses) [29] and by inhibiting the MHC-II expression [30], statins promote the reactivation of VZV replication which finally leads to HZ. Moreover, other mechanisms are probably involved since most of the patients with HZ have often comorbidities

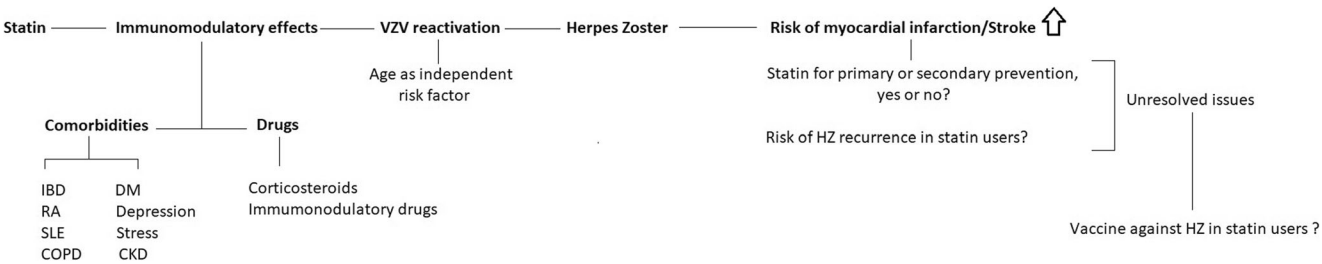

Fig. 2 Suggested series of events from the statin assumption to the onset of herpes zoster. VZV, varicella zoster virus; HZ, herpes zoster; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease. After an HZ, a higher risk of cardiovascular events has been reported. In these patients, to date, there is no consensus regarding the assumption of statin alone or after receiving a vaccine against zoster

Table 3 Possible effects of statins in inducing HZ infection

Effects of statins	Possible mechanisms of HZ infection
Inhibition of HMG-CoA reductase decreases the synthesis of isoprenoid pyrophosphates, required for the activation of Ras-related GTPases	T cell activation and proliferation are impaired
Block the effect of leucocyte function-associated antigen 1 and affect leukocyte endothelial interaction	Dysregulate immune response
Increase the number of $CD4^+CD25^+$ T cells	Their accumulation contributes to the age-related immunosenescence and reactivation of latent infectious diseases
Promotion of Th2-cell differentiation	Suppression of Th1-type immune responses involved in controlling VZV replication
Inhibit interferon-γ-induced MHC-II expression	Possible reactivation of VZV

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; *MHC*, major histocompatibility complex; *VZV*, varicella zoster virus; *HZ*, herpes zoster

which required some drugs with immunomodulatory effects, such as corticosteroids in patients with RA, IBD, SLE or cancer. Further studies, therefore, are needed to better explain the biochemical relationship among statins, VZV and HZ. Future in vitro and in vivo studies should analyse both the potential risk factors and the antigenic mechanisms involved in VZV reactivation, allowing an individual and/or population vaccination program, especially in those patients requiring a statin treatment. The reviewed studies presented herein show some limitations and several drawbacks that must be clarified. First, patients were randomised as statin users or non-users, irrespective of the type of molecule, potency or chemical-physical characteristics (lipophilic or hydrophilic), which could affect the immunomodulation of the drug. Specific studies, therefore, enrolling patients treated with different type of statins are required to further elucidate this aspect. Secondly, the analyses did not report the reason of statin prescription, i.e. because of primary or secondary prevention, primary dyslipidaemia or metabolic syndrome (MS). To this regard, for example, MS might play an important role in the reactivation of VZV infection. In fact, MS showed an unexpected relationship with several infectious diseases and a dynamic interplay with immunity [31]. On the other hand, MS patients greatly benefit from appropriate interventions of cardiovascular prevention and correction of the cardiovascular risk factors, such as statin therapy, which increases the risk of VZV reactivation. Moreover, a higher incidence of cardiovascular events has been reported after HZ [20, 21]. Therefore, questions remain: how to manage the cardiovascular risk after HZ and how to apply an effective cardiovascular prevention strategy, including statin therapy, without increasing HZ risk? Considering the clinical complexity of most patients, the presence of comorbidities, the requirement of a tailored and personalised treatment, a careful evaluation of the potential risks and benefits is mandatory by a multidisciplinary approach, which involved different professionals such as the specialist in infectious diseases, the neurologist and the cardiologist. In this setting, high cardiovascular risk patients who require statin therapy should probably be treated with HZ vaccine. Finally, since risk factors for HZ infection can suppress immune responses to vaccination against HZ and statins, for example, have been associated with a reduced efficacy of influenza vaccination, further studies are needed to assess whether statins can decrease immune responses to vaccination against HZ, as suggested by others [7].

Conclusions

Statins can increase the odds of developing HZ. However, as recently described, statin-related benefits in cardiovascular prevention indubitably outweigh the potential risks, as the described mild increase risk of HZ. Consequently, this novel potential adverse event of statins would not be expected to alter the balance of benefits and harms. Current available data must be considered as preliminary, since there is a risk of an increased reticence among the physicians to prescribe statins and to reduce the patient's compliance due to raised awareness of perceived side effects [32].

On the other hand, the relationship between statins and HZ must be kept into account both during the acute phase and PHN by the infectious disease specialist, neurologist and in the long-term period by the general practitioner. Further studies are needed to explain, more carefully, the immune-modulating effects of stains, especially in VZV reactivation, to identify those patients at higher risk of HZ and, as consequence, plan individual or population vaccination programs. Indeed, in selected statin users, vaccination against HZ seems to be a valid solution, but more conclusive observations are required to assess if statins decrease the immune responses to vaccination against HZ.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not required for a review article.

Informed consent Not required for a review article.

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