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Proceeding Paper

Antimicrobial Potential of Hydroxymethylglutaryl-Coa Reductases Inhibitors †

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Abstract: This study proposes the contemplation of an ecumenical scenario on the antimicrobial potential of statins, based on a scientific narrative review, providing subsidies for research and possibilities in the face of this public health problem. To start the investigation, a guiding question was elaborated to conduct the entire research process, using the PICo strategy (population/interest/context). The results reveal the antimicrobial potential of statins against different strains. The activity appears to be statin-specific/ bacteria-specific, with an emphasis on simvastatin and atorvastatin, and Gram-positive bacteria, as well as an adjuvant activity to rifampicin in the fight against mycobacteria.

Keywords: statins; antimicrobial; microbiology

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1. Introduction

Bacterial resistance to antibiotics represents a serious and worrying public health problem worldwide. From the 1970s onwards, a dizzying outbreak of resistant bacterial strains, especially in hospitals, gave scholars a new look at the indiscriminate use of antimicrobials, since this was the main factor pointed out in the occurrence of this problem. This condition is defined as the ability of a bacterium to grow in the presence of drug concentrations that should inhibit this microorganism, in vitro [1].

There are two possible classifications: First, there is the intrinsic type, which is when this resistance already naturally exists due to the primitive genetic characteristics of the microorganisms, evidenced, for example, through structures or mechanisms that prevent the antibiotic from acting on its specific receptor, due to the coding of chromosomal genes. The second class is acquired resistance, which occurs in initially sensitive bacteria, which, due to mutations, transductions, transformation and conjugation, acquire this characteristic [2].

Considering this scenario, the reuse of drugs already known is presented as a quick and less expensive opportunity, being considered an attractive alternative for the development of new drugs and treatments [3]. This is possible due to the pleitropic effects, which are relevant implications in areas other than those that are initially applied. An example of this is the hydroxymethylglutaryl-CoA reductases (HMG-CoA) inhibitors, known as statins, which have relevant potential in several areas such as antithrombotic, antioxidant protection, immunomodulatory and anti-inflammatory activity [4].

Studies have shown prominent participation in hospital infection scenarios, especially in the prevention and management of sepsis diagnoses. Thus, questions about these drugs against bacterial strains have been considered as a wide field for exploration in laboratory and clinical research [5]. Therefore, this study proposes the contemplation of an ecumenical scenario on the antimicrobial potential of statins; in this context, its objective is to carry out

a narrative review of the scientific literature, providing a basis for future research and new possibilities in the face of this public health problem.

2. Materials and Methods

This is a theoretical research, characterized by a qualitative approach, of an exploratory descriptive type. Narrative review was used as a method to conceive the state of the art and support a pertinent appreciation of the theme. A broad analysis of the scientific bibliography was carried out with the purpose of acquiring knowledge and collecting the main considerations, focusing on the innovations discovered and highlighted in the selected literature. To initiate the investigation, a guiding question was prepared to conduct the entire research process, using the PICo strategy (population/interest/context).

Thus, the following question was presented: "what is the antimicrobial potential (I) of statins (P) referenced in the scientific literature (Co)?" Then, the bibliographic search started, during January 2021, in the databases destined to index journals and scientific articles. "Statins" were used as descriptors and search terms: "Antibacterial activity", combined with the Boolean AND operator. A time interval was not determined; however, recent studies were prioritized. Works were selected that explicitly portrayed in their summary or title that the text relates to the potential and activities of statins against bacterial strains.

Works published in the format of scientific articles were preferable. Articles published in Portuguese, English and Spanish were accepted. The exclusion occurred in the face of articles that did not present the results of the research in full, duplicates, or that the body of the text did not match or answer the guiding question of this study, resulting in eight eligible articles. Then, the selected works were read in full, highlighting the main contributions of statins in relation to antibacterial activity.

After the individual study of each work, the construction of the state of the art began, aiming to answer the research question. There was no need to use judges to perform a qualitative treatment of the extracted data, due to the type of methodology chosen, while submission to the research ethics committee was also not necessary, since the samples were obtained from data already published and available publicly.

3. Results and Discussion

Statins act as selective and reversible inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, being used clinically in the drug therapy of dyslipidemias. Considering the observations acquired on the various clinical effects obtained with the use of these drugs, researchers began to investigate new clinical possibilities considering the pleitropic effects of this class of drugs [5]. In this perspective, studies on the antimicrobial capacity of these drugs have come to stand out in the scientific community.

Evaluations of three statins against the growth and viability of species of *S. aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Enterococcus faecalis* were performed. After studying the effects of artovastatin, pravastatin and simvastatin, only the latter showed bacterial activity, with the ability to inhibit and destroy biofilm similar to the effects of vancomycin and gentamicin, being the strain most sensitive to *S. aureus*, with the minimum inhibitory concentration between 15, 6 and 31.25 µg/mL [6].

Still considering bacterial biofilm, while being multispecies, simvastatin showed, in another investigation, it had a greater capacity to inhibit this biofilm, affecting the viability and proportion of bacteria, when compared to the results of atorvastatin, fluvastatin and lovastatin; additionally, it had the effect of reducing 1300 times the bacteria *Porphyromonas gingivalis* in relation to the control group. In this study, this strain also showed greater sensitivity to lovastatin, when compared to the other species studied: *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Actinomyces naeslundii*, *Tannerella forsythia* and *Streptococcus gordonii* [7].

An in vitro study evaluated the bacterial activity of statins against different strains of the American Type Culture Collection (ATCC) and ten cultures of clinical isolates. As reported in other investigations, this study showed a greater sensitivity of Gram-positive

bacteria to the action of statins, with the highlight being the activity of atorvastatin and, above all, simvastatin [8].

Another highlight is the use of statins to treat mycobacterial infections. A group of researchers investigated the efficacy of simvastatin and atorvastatin on intracellular viability in macrophages of *Mycobacterium bovis*, *M. leprae* and *M. tuberculosis*, as well as the effect on *Mycobacterium leprae* infection in mice. The combination of statins with rifampicin showed a considerable decrease in bacterial intracellular viability, just as atorvastatin was effective in controlling *M. leprae* infection in mice [9].

There is still no definite explanation about the antibacterial activity of these drugs; however, scholars make associations that aim to justify these effects. One hypothesis is the direct linkage of the methyl groups of statins with teicoic and lipoteic acids of Gram-positive peptide glycols, being associated with alanine residues causing structural distortions, resulting in a deprotection of the bacterial framework [10]. The promotion of disruptions of weak bonds in lipopolysaccharides and proteins of the Gram-positive and Gram-negative bacterial surface are still considered, such as hydrogen bridges and Van der Waals forces, preventing bacterial proliferation, acting with bacteriostatic function [10,11].

Another point that deserves attention is that the *S. aureus bacterium* obtains isoprenoids from the catalytic action of HMG-CoA reductase, in the mevalonate pathway, which may justify the greater sensitivity of the strains of this bacterium to HMG-CoA inhibitors, when compared to *E. coli* and *P. aeruginosa*, which use another route to acquire these metabolites [12].

4. Conclusions

The scientific literature presents studies that reveal the antimicrobial potential of statins against different bacterial strains. The antibacterial activity appears to be statin-specific/bacteria-specific, with an emphasis on simvastatin and atorvastatin, and Gram-positive bacteria, particularly *S. aureus*. Research reveals a potential similar to that obtained with antibiotics used in clinical practice, as well as an adjuvant action, increasing the effect of rifampicin in the treatment of mycobacterial infections.

This study reveals the need for more rigorous clinical investigations, as well as epidemiological studies for a better glimpse of the viability of statins against bacterial infections. Thus, it can serve as an indication for the development of new therapeutic possibilities, reducing the use of antibiotics in the clinical routine.

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