Atorvastatin: 2nd Generation HMG-CoA Reductase Inhibitor

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Abstract

In 2008, sales for atorvastatin (Lipitor) exceeded 12.4 billion dollars, making it the top-selling brand name pharmaceutical product in the world.[1] Atorvastatin is in a class of drugs known as HMG-CoA reductase inhibitors, or statins, and is used in patients to lower "bad" cholesterol levels (specifically LDL levels) by inhibiting the enzyme HMG-CoA reductase.[1] Reduced cholesterol levels diminish the risk of heart complications, such as coronary artery disease, heart attack and stroke. In addition, atorvastatin is one of five statins cleared by the liver via cytochrome P450 enzymes. As with this and other statins, side effects such as muscle weakness (myopathy) and liver toxicity are possible and prompt for future drug development centering on patient safety and efficacy.

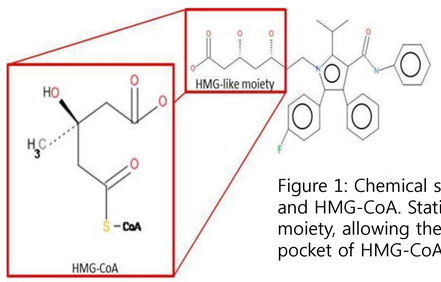

Figure 1: Chemical structures of atorvastatin and HMG-CoA. Statins possess an HMG-like moiety, allowing them to fit in the binding pocket of HMG-CoA reductase.

Introduction

With the increasing prevalence of cardiovascular-related events occurring in the United States, management of cholesterol (especially LDL levels) is critical. Statin therapy is the most common and effective way to decrease LDL levels. Atorvastatin is timely highlighted since it has just become available generically and is more effective at reducing LDL levels compared to many other statins (it is considered a "high potency" statin).

When HMG-CoA reductase functions normally in the body, it plays a role in cholesterol synthesis in the liver. Cholesterol aids in hormone production, digestion, and cell structure.[2] When HMG-CoA reductase produces too much cholesterol it causes hyperlipidemia, which is the primary risk factor for coronary artery disease and other cardiovascular-related events. Interestingly, HMG-CoA reductase favors binding to atorvastatin over its natural substrate, mevalonate.[3]

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Molecular Story

Atorvastatin prevents the conversion of HMG-CoA to mevalonate which is an important step in cholesterol synthesis (Figure 1).[4]

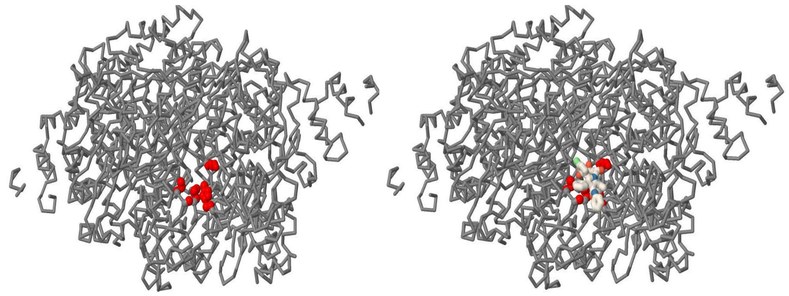


Figure 2. Competitive inhibition of HMG-CoA reductase by atorvastatin

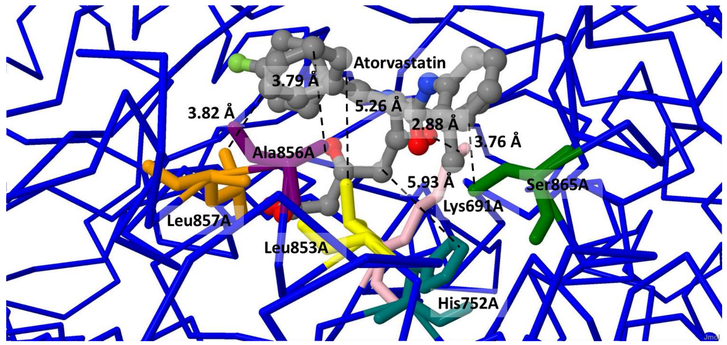
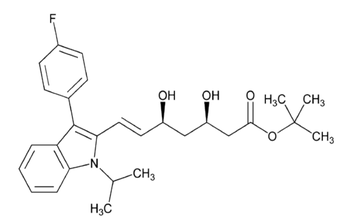
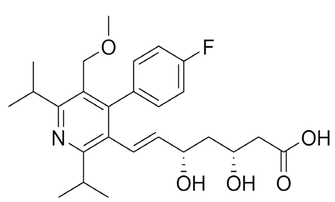


Figure 3: Atorvastatin bound to HMG-CoA reductase binding site

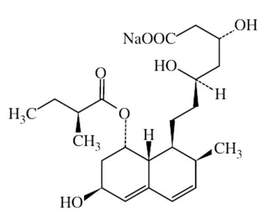
HMG-CoA reductase is composed of four subunits and it interacts with atorvastatin most significantly through ionic or polar interactions (Figure 2).[5] The two major binding sites are the hydrogen bond between Lysine 691 to the O5 hydroxyl oxygen on atorvastatin and Serine 565 to the O18 carbonyl oxygen of atorvastatin (Figure 3).[6]



Fluvastatin



Cervistatin



Pravastatin

Figure 4. Fluvastatin and pravastatin, two water attracting statins in comparison to cervistatin, a highly water repelling statin.

The Next Step in Drug Design

Studies have linked the side effect myopathy to ubiquinone protease pathway, a protein degradation pathway.[6] An explanation is that statins embed into skeletal muscle cell (myocyte) membranes and cause instability. This instability activates a cascade leading to up-regulation of the ubiquinone protease pathway and thus, greater protein turnover rates in skeletal myocytes.[7]

Changing the structure of atorvastatin could lower the incidence of myalgia. What should not be changed is the HMG-like moiety, which gives all statins their specificity for HMG-CoA reductase. Atorvastatin is hydrophobic (water repelling) because of its three aromatic rings attached to a central pyrrole ring (Figure 1).[7] This enables atorvastatin to easily embed into myocyte membranes. This can potentially be prevented by removing one, two, or all of the aromatic rings, thus making atorvastatin a more hydrophilic (water attracting) statin. Potency would not change drastically because hydrophilic statins can enter hepatocytes (liver cells) through membrane transporters. Removing the aromatic rings is possible because pravastatin and fluvastatin are considered hydrophilic statins and have the lowest incidence of myalgia. Cervistatin, on the other hand, being the most hydrophobic of statins, caused such a high incidence of adverse effects that it was pulled from the market (Figure 4).[6]

Summary

As cardiovascular-related events continue to rise, the need for cholesterol lowering therapy becomes a necessity and requires knowledgeable pharmacists to educate patients on benefits for early initiation of statin agents. While other statins have been the initial drug therapy for many patients in the past, the recent advent of generic atorvastatin will bring forth more affordable options for physicians and pharmacists alike to choose from in order to provide better patient care.

References

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