

Seymour Katz, M.D., Series Editor

Statins Reduce Inflammation, DVT, Osteoporosis, and Colon Cancer: Could They Be of Benefit in IBD?



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Cholesterol-lowering statin medications have surprising beneficial effects beyond their original indication. Evidence of anti-inflammatory, anti-thrombotic, anti-osteoporotic, and anti-cancer effects of statins suggests that these medications may have additional therapeutic uses. Statins are particularly appealing for inflammatory bowel disease, as IBD patients have intestinal inflammation, increased risk of deep venous thrombosis, increased risk of osteoporosis, and increased risk of colon cancer. Statins are relatively safe, and are becoming less expensive as they become available in generic form. Prospective randomized clinical trials are required to demonstrate whether statin use produces measurable benefits in patients with IBD.

BACKGROUND

Statin medications lower serum cholesterol by competitively inhibiting HMG-CoA reductase. By this mechanism, statins effectively lower LDL cholesterol and reduce the risk of ischemic heart

disease and stroke. The relative safety of statins has led to their widespread use, but recent research suggests that statins may have additional important therapeutic effects via other molecular pathways (1,2). We will outline our growing understanding of the mechanisms of statins, review the safety record of statins, and detail the effects of statins in inflammation, thrombosis, osteoporosis, cancer, and inflammatory bowel disease.

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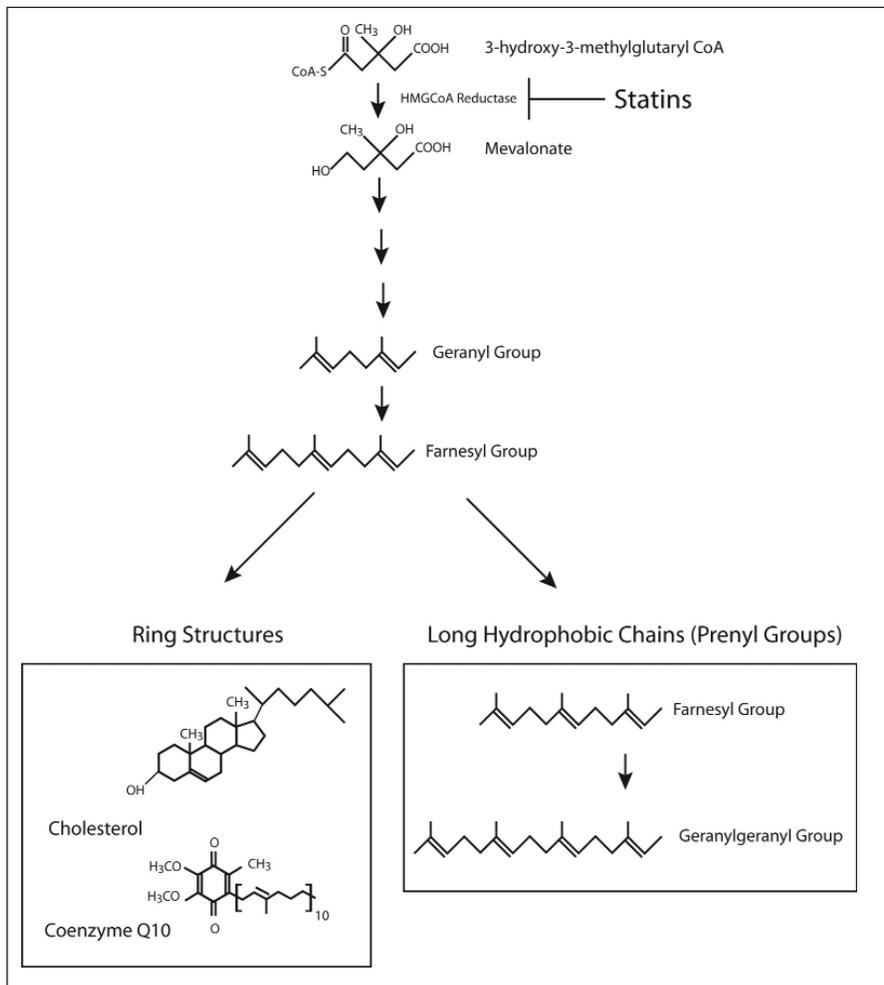


Figure 1. Statin Effects on the Mevalonate Pathway. Statins inhibit the production of mevalonate, which can be processed either into ring structures like cholesterol or coenzyme Q10, or into long hydrophobic chains (prenyl groups).

MECHANISMS OF STATINS

Statins lower serum cholesterol by competitively inhibiting HMG-CoA reductase, the rate-limiting enzyme in the synthesis of mevalonate, an essential intermediate in cholesterol biosynthesis (Figure 1). Mevalonate can be used to make either hydrophobic ring structures (i.e. cholesterol, ubiquinone [aka Coenzyme Q10]) or long hydrophobic chains (prenyl groups). Statins inhibit and affect both pathways, and this inhibition produces biologic effects in each pathway.

The long hydrophobic chains, or prenyl groups, are attached to small cellular membrane signaling pro-

teins including Rho and Ras. This prenylation is essential for these small G proteins to anchor to the cell membrane and to perform their cell signaling functions. Rho activation stimulates the pro-inflammatory transcription factor NF-kappa B, which drives inflammation and inhibits apoptosis, and Ras activation is linked to colon cancer. The inhibition of prenylation of G proteins by statins may explain why statins have beneficial effects on inflammation and cancer (3–5).

SAFETY OF STATINS

Statins are relatively safe drugs, leading to their over the counter status in the United Kingdom, but they do have known side effects. Statins have been shown to cause elevated liver function tests in approximately 1%–3% of patients. These test abnormalities are reversible, and no cases of liver failure have occurred. Statins can induce muscle soreness, and even rhabdomyolysis in 0.1% of patients (6). This is generally reversible with discontinuation of the drug, though some evidence suggests that supplementation with coenzyme Q10 may reduce the incidence or shorten the time to recovery from rhabdomyolysis (7). Rare cases of death from rhabdomyolysis have been reported. One rare colonic side effect has been reported for statins—they can rarely cause a reversible drug-induced colitis (8). A case series of 8 patients suggests that significant amounts of statin medications reach the colonic epithelium and can cause toxicity. In the laboratory, statins can cause a similar dose-dependent toxicity in colonic epithelial cells, suggesting that this is could be a local toxic effect of high doses of statins in susceptible patients. On the whole, statins have a remarkable safety record despite extensive use in patients with significant morbidities.

EFFECTS OF STATINS ON INFLAMMATION AND MICROPARTICLES

Inflammation plays a critical role in the pathogenesis of many chronic human diseases, including coronary atherosclerosis, cancer, and neurodegenerative diseases. Statins have potent anti-inflammatory properties that are directly related to their therapeutic effects. The beneficial effect of statins on cardiovascular disease (CVD) has been linked to elevated markers of systemic inflammation. Patients with elevated C-reactive protein (CRP) but normal cholesterol levels have decreased cardiovascular events while on statins(9). This suggests that statins act through cholesterol-independent pathways to reduce inflammation, stabilize inflamed atherosclerotic plaques, and prevent plaque rupture and coronary occlusion. More generally, patients with elevated CRP levels derive greater benefit from statin therapy than those with low CRP levels, regardless of their LDL cholesterol levels (10).

Investigation of the anti-inflammatory effects of statins led to the discovery of biologic effects that are independent of statins' effects on cholesterol. The inhibition of the prenylation of Rho, and the subsequent inhibition of the pro-inflammatory transcription factor NF-kappa B, leads to inhibition of many downstream inflammatory mediators. Statins inhibit the production of inflammatory mediators such as IL-12, interferon gamma, interleukin 1 β , interleukin 6, and tumor necrosis factor α (11–14). All of these effects are potentially beneficial in inflammatory bowel disease.

Statins also affect the generation of microparticles through their inhibition of Rho. Microparticles are small (0.2–1 micron diameter) particles that increase leukocyte and platelet adhesion, stimulate inflammation and leukocyte translocation into tissues, and stimulate thrombosis. They are consistently elevated in inflammatory disease states, such as sepsis, CVD, and multiple sclerosis (15–17). Recent reports suggest that platelet microparticles are elevated in active IBD (18,19). Statins have been shown to decrease microparticle release, and statins have beneficial effects on diseases associated with elevated microparticles. Statins may produce some of their anti-inflammatory and anti-thrombotic effects through the inhibition of microparticle release. While this physiological evidence of anti-inflammatory effects of statins is

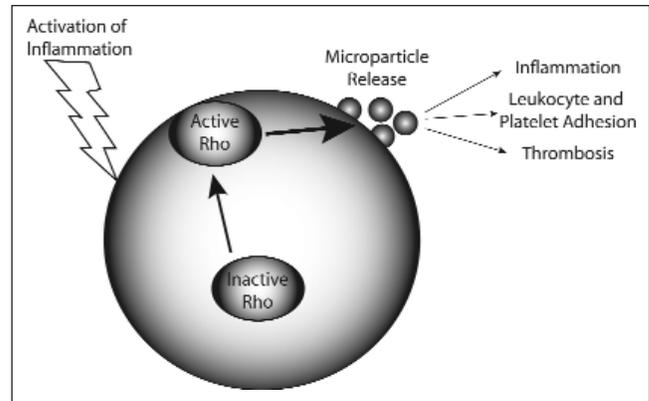


Figure 2. *Inflammation Stimulates Rho and Microparticle Release.* When pro-inflammatory signals like interleukin-1 or tumor necrosis factor alpha activate leukocytes, platelets, or endothelial cells, this causes increased activation and signaling by Rho proteins, which are prenylated and attached to the cell membrane. This leads to release of microparticles, which can increase inflammation, increase adhesion of leukocytes and platelets to the endothelium of blood vessels, and stimulate thrombosis. Statins have been shown to decrease Rho signaling and decrease microparticle release.

encouraging, it is not convincing evidence of clinical benefit in inflammatory diseases.

EFFECTS OF STATINS IN INFLAMMATORY DISEASES IN HUMANS

There is growing evidence that statins may be beneficial in patients with a variety of inflammatory states. In an observational study of patients with proven bacterial sepsis, patients who were on statins and continued them while in the hospital had decreased mortality (23% versus 2%) compared with patients who never used statins (20) (Figure 2). Patients with multiple sclerosis have been shown to have a reduction in lesions detectable by MRI in an open-label study of simvastatin (21). In patients with rheumatoid arthritis, statins produced improvements in tender joint counts and inflammatory markers, and moderate improvements in symptoms (22,23). Although these data cumulatively suggest a general beneficial effect of statins in inflammatory diseases, additional randomized prospective controlled trials are needed, and direct evidence of benefit in IBD is still lacking.

INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH, SERIES #19

Table 1.
Statin use and risk of colorectal cancer in sporadic and IBD-associated colon cancer

<i>Patient Sample</i>	<i>Statin Use</i>	<i>Cancer Cases</i>	<i>Controls Without Cancer</i>	<i>Total</i>	<i>Odds Ratio</i>
Sporadic CRC	Yes	120	234	354	0.53
	No	1833	1781	3614	(0.40–0.63)
IBD	Yes	1	5	6	0.06
	No	38	11	49	(0.006–0.55)

EFFECTS OF STATINS ON DEEP VEIN THROMBOSIS (DVT) PREVENTION

Patients with inflammatory bowel disease have a 3-fold increased risk of DVT for reasons that remain unclear, but this increased risk appears to be associated with active inflammation (24,25). Platelet microparticles have been found to be elevated in murine models and humans in the setting of deep vein thrombosis (DVT), and these microparticles increase the risk of DVT. Statins have been shown to decrease microparticle release (26) and recent studies have shown that statin therapy can reduce the risk of DVT in humans. In a retrospective cohort study of elderly patients, statins were associated with a 22% relative risk reduction for DVT (27). This appears to be a secondary benefit of statins that is independent of cholesterol lowering, and is not seen in patients using non-statin cholesterol-lowering medications.

EFFECTS OF STATINS ON BONES

Osteoporosis is a common problem in patients with severe IBD, and particularly in those who have required multiple courses of steroids. In a drug-discovery screening program, lovastatin was identified as a drug able to stimulate new bone growth by stimulating bone morphogenetic protein 2 (28). Several observational studies and a recent meta-analysis demonstrated that statin use is associated with reductions in fracture rates (29). Short prospective studies have found improvements in bone mineral density with simvastatin (30). A secondary effect of statins to improve bone mineral density or decrease fracture risk

could be beneficial in patients with IBD if proven in randomized controlled trials.

EFFECTS ON COLON CANCER

Statins cause programmed cell death of colon cancer cells in the laboratory. This is due to the inhibition of the prenylation of the G protein Rho(1). Statins also have anti-tumor effects in rodent models of colon cancer. Statins can prevent chemical-induced colon tumorigenesis in rats (31,32), and inhibit metastases in murine colon tumor models (33). There is also recent evidence of statin effects in human colon cancer. Poynter, et al showed that use of statins for at least 5 years was associated with a 47% reduction in sporadic colon cancer, and a 94% reduction in colon cancer in patients with IBD (Table 1) (34). While these dramatic results in the IBD patients may merely reflect the small sample size, the anti-inflammatory and pro-apoptotic effects of statins may make statins especially effective for chemoprevention in patients with IBD.

A subsequent study by Rubin evaluated use of statins during a one year period and found a trend toward colon cancer reduction in IBD patients exposed to statins (22%), but this was not statistically significant (35). This may be interpreted as evidence of no effect, or may suggest that several years of regular statin use, as in Poynter’s study, are necessary for a significant anti-cancer effect. This observational effect needs to be confirmed in prospective studies of cancer prevention.

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PRECLINICAL AND CASE SERIES EVIDENCE OF STATIN EFFECTS ON IBD

Recent studies of statins have shown some evidence of benefit in animal models of IBD. Sasaki used the dextran sulfate sodium (DSS) model of colitis to demonstrate that intestinal injury and symptoms were ameliorated by statins (36). A second study by Nam showed benefit of either simvastatin or atorvastatin in the DSS colitis model (37). These studies suggest that statins may be of benefit in IBD. In the only study to date in humans, Hibi reported at Digestive Disease Week 2002 a case series of patients with ulcerative colitis who improved substantially with atorvastatin therapy. This was an open-label, uncontrolled study that has not yet been published, but showed substantial benefit in seven patients with ulcerative colitis (38).

LACK OF EVIDENCE OF STATIN EFFICACY IN HUMANS FOR IBD

Despite this suggestive data, there are currently no published randomized trials that have tested the efficacy of statins as therapeutic agents in IBD. Randomized controlled trials are needed to explore the potential benefits of statin therapy. Anecdotal reports from our IBD clinic patients suggest that: 1) most patients who do notice improvement with statins find it occurs slowly, over months, and 2) not everyone with IBD on a statin improves.

Our group has initiated a pilot study of atorvastatin in ulcerative colitis. We designed this study as a 24-week randomized controlled trial of 36 subjects to detect improvement with a slow onset. We will also try to determine whether there may be a subset of patients most likely to benefit from statin therapy by measuring baseline variables in subjects that may predict which patients will respond to statins, including ANCA ASCA, and OmpC serologies, duration and extent of disease, and baseline CRP (Figure 3).

CONCLUSIONS

There is substantial preclinical evidence of the anti-inflammatory effects of statins, and a variety of clinical evidence of beneficial effects in inflammatory diseases other than IBD in humans. These effects of statins

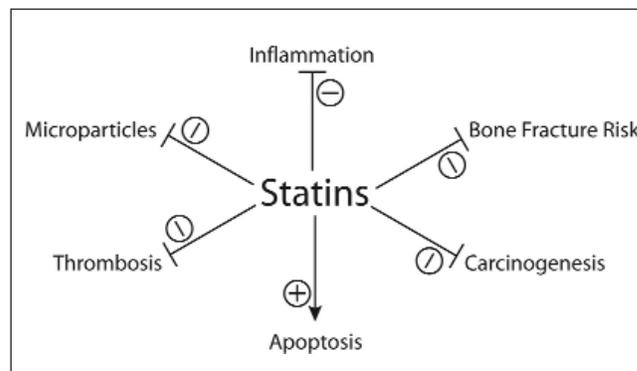


Figure 3. *The Pleiotropic Effects of Statins.* Statins inhibit inflammation, and appear to have beneficial effects through inhibition of biological processes that appear to be stimulated by inflammation, including microparticle release, thrombosis, osteoporosis, and carcinogenesis. Statins also stimulate programmed cell death, or apoptosis, of colon cancer cells.

appear to be due to the inhibition of prenylation of Rho proteins, and are mechanistically independent of cholesterol lowering. The reported secondary benefits of statins in preventing DVT, preventing osteoporosis and fracture, and preventing colon cancer could be beneficial for IBD patients, but are largely from observational studies, and need to be tested with prospective trials. Rare reports of colitis associated with statin use suggest that some patients could have a drug-induced colitis from statins, and statins could thereby possibly produce harm in IBD patients. While statins are appealing medications for inflammatory bowel disease, there is not yet solid evidence of their efficacy in IBD, and prospective studies of statins in patients with inflammatory bowel disease are needed. ■

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