

Use of 20mg statins (atorvastatin/simvastatin) as a novel new option of medically treating fibroids—overcoming the drawback of selective progesterone receptor modulators of interruption before long term use

Short communication

Uterine fibroids are the most common benign tumours in women with a lifelong incidence of approximately 75%.^{1,2} Roughly 25-50% of women affected with Uterine fibroids develop symptoms like menorrhagia, pelvic pain, pelvic pressure along with infertility and pregnancy complications.^{1,2} Hysterectomy is the main curative treatment, but being costly, invasive and resulting in loss of child bearing capacity, women desiring future fertility, or those being poor candidates for surgery don't desire the same. Hence need for nonsurgical anti Uterine fibroid therapies, are needed for women desiring fertility. Long term therapies trying to decrease uterine fibroid size along with helping in get over the symptoms are required that are safe, cost effective without interfering with future fertility.³

Oral, long term treatment options for Uterine fibroids have been introduced recently. These are 2 family of compounds namely i) gonadotropin releasing hormone antagonists like Elagolix, Relugolix, and OBE2109, and ii) selective progesterone receptor modulator (SPRM's), like ulipristal acetate(UA), vilaprisan, and Proellex.³ Most of these drugs are under clinical trials. Although UA has received approval by both the European Medical Agency and US Foods and Drug Administration (FDA) and is being used for treating Uterine fibroids in Europe and Canada. Since UA is not marketed in countries like India we are forced to use the 1st generation SPRM, namely mifepristone in those not wanting hysterectomy.⁴

With the initial studies it was proved that these drugs decrease fibroid size, reduce bleeding, and improve anaemia in a variety of patient populations that are representative of women most affected by Uterine fibroids. However few limitations hinder the long term use of these medicines. Like Elagolix needs to be taken with add back therapy for preventing hypoestrogenic side effects like hot flushes and bone density loss, that might decrease its working efficiency. Although SPRM's had promising anti uterine fibroid effects, in view of benign endometrial changes also called progesterone(P) associated endometrial changes(PAEC's), long term use gets limited, needing to discontinue the drug for some time.³

Statins are a drug family basically used for hyperlipidemia. They inhibit 3-hydroxyl-3methyl glutaryl coenzyme A(HMG-CoA) reductase and hence prevent the conversion of HMG-CoA to mevalonate and hence=>dramatic decreases in both cholesterol and its isoprenoid precursors; farnesyl pyrophosphate(FPP) and geranyl geranyl pyrophosphate(GGPP).^{5,6} Statins have been there since 1980 in the market. They have been employed for various cancers in view of a pleiotropic effect. Since statins inhibit steroidogenesis and thereby decrease estradiol (E2) and progesterone (P), they remove the E2/P supply of Uterine fibroid which makes them important drugs to

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be tried as novel agents to medically treat these uterine fibroids.

Recently Malik et al.⁷ showed that simvastatin inhibits fibroid proliferation, causes apoptosis along with reducing extra cellular matrix (ECM) production by uterine fibroid cells. Earlier Borahay tested the antifibroid effect of simvastatin in lower concentrations i.e. in the nanomolar range. Malik showed that 48hrs following simvastatin, an effective antiproliferative effect was seen on uterine fibroid cells only sparing the matched myometrial cells at the classically relevant range of 10⁻⁹-10⁻⁷nM. Higher concentrations were toxic for both cell types. Borahay who had been studying fibroid development and effects of simvastatin showed that simvastatin acted by reducing mitogen activated protein kinase (MAPK) and protein kinase B signaling pathway phosphorylation along with inducing Calcium dependent apoptosis of uterine fibroid cells both *in vivo* and *in vitro* along with increasing caspase -3 activity, particularly at micromolar levels of 0.1-10µM.^{8,9} To examine further the anti- uterine fibroid effects of treatment with simvastatin *in vivo* using immuno deficient mice xenografted with human uterine fibroid tissue, they supplemented mice with E2/P pellets to mimic the hormone effects on Uterine fibroids^{8,9} initially. This was followed by treatment with simvastatin at a dose of 20µg/g body weight/day for 28days and they reported that simvastatin significantly inhibited fibroid tumor growth¹⁰ Subsequently they carried out a nested case control study of >190,000 women to analyze the relation between use of statins at antihyperlipidemic doses and the risk of development of Uterine fibroid/ Uterine fibroid related symptoms.¹⁰ Use of statins correlated with lower odds ratio of developing uterine fibroid, menorrhagia, anemia, pelvic pain or myomectomy in contrast to non users.⁸

Subsequently Shen conducted a retrospective study in 120 patients having fibroid with hyperlipidemia where atorvastatin 20mg/day was

used for 1-2yrs significantly suppressed growth of uterine fibroids. This effect was found in dose and time dependent manner and was by apoptosis of uterine fibroid cells by inducing caspase -3 activation, up regulation of Bim and down regulating Bcl2. Also suppression of phosphorylation of ERK1/2 and JNK was reported. Moreover GGPP, a downstream lipid isoprenoid intermediate significantly rescued the effects of atorvastatin and claimed the 1st clinical as well as preclinical data on use of atorvastatin as a promising nonsurgical method for treating uterine fibroids.¹¹

As per Bjorkhem-Bergman et al.,¹² there was a large difference between the statin concentrations used in cells *in vitro* experiments and those found in human plasma. They reported pharmacokinetic data that 40mg of simvastatin produces a mean serum concentration of 2.2-4.3nM and the highest concentration of 19-31nM, although its pleiotropic effect is examined *in vitro* using micromolar concentrations. Malik showed the anti uterine fibroids effect was seen in the nanomolar range 10^{-9} – 10^{-7} nM report as per a letter to editor regarding Bergman's findings that smaller concentrations are needed. Thus a potential role of simvastatin for treating uterine fibroids, at the clinical hyperlipidemia uses help since that dose is already approved by FDA regarding hyperlipidemia. The commonest side effects of statins are muscle pain, gastrointestinal(GIT) upset and headache. The most severe ones, namely rhabdomyolysis and liver damage are rare.

One novelty of Malik's study⁷ was the examination of 3 dimensional (D) fibroid culture model, since this mimics the *in vivo* microenvironment most closely *in vitro* system. This 3D cell culture maintains the molecular phenotype of uterine fibroids, with the interaction of the extracellular matrix, that is not available in 2D culture systems. Next step is studying simvastatin in animal models of uterine fibroids using doses, equivalent to the *in vitro* nanomolar concentrations, before a prospective human clinical trial can be started. In view of increased body mass index (BMI) being a risk factor for both Uterine fibroids and hyperlipidemia, overweight/obese women having symptomatic uterine fibroids and hyperlipidemia might serve a dual purpose treatment option in the long run and hold the novel therapy we have been looking for continuous long therapy not needing a break like the SPRM'S in view of PAEC's.

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Conflicts of interest

The authors declared there is no conflict of interest.

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