BEYOND THE HORIZON: NOVEL & DEVELOPING MEDICAL STRATEGIES FOR FIBROIDS

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DISCLOSURES

• I am a primary investigator on past and current medical trials with:
• I have been a member of an advisory board with:
• I have presented or spoken in CME events sponsored by:
  • Abbvie
  • Bayer
  • Allergan
OBJECTIVES

• Introduce the current landscape for treatment options

• Provide an overview of novel, early development therapies for uterine fibroids

• Update on upcoming SPRM trials
WHY DO WE NEED NEW OPTIONS?

“Choice is the epitome of freedom”
8 Natural Treatments for Fibroids

1. Avoid foods that make fibroids worse.
2. Eat foods that help relieve fibroids.
3. Try supplements that aid in fibroid reduction.
4. Turn to essential oils.
5. Sip on herbal teas.
6. Try castor oil packs.
7. Avoid exposure to environmental toxins.
8. Exercise.

Fibroids: 8 Ways to Manage or Prevent Uterine Fibroids - Dr. Axe
https://draxe.com/fibroids/
8 Ways to Naturally Prevent & Relieve UTERINE FIBROIDS
2. Eat Foods that Help Relieve Fibroids

What type of diet can help prevent or treat fibroids? The following foods should be included in your diet to keep them at bay:

- **Organic Foods.** Eating mostly organic foods may help to prevent and shrink fibroids because organic products are grown and made without the use of chemical presesticides. Pesticides used in commercial/non-organic agriculture may impact estrogen levels and other hormones. Since hormonal balance is key to natural fibroid treatment, you want to reduce your pesticide intake as much as possible.

- **Green Leafy Vegetables.** Green leafy vegetables have many anti-inflammatory effects, so they may discourage the growth of fibroids in a woman’s body. These vegetables are also vitamin K-rich foods, which aid in blood clotting and help control menstrual bleeding.

- **Cruciferous Vegetables.** **Cruciferous vegetables** support detoxification of your liver and may help balance estrogen levels. Research has shown that high consumption of broccoli, cabbage, Chinese cabbage, tomato and others may decrease the risk of estrogen-fueled fibroids.
3. Try Supplements That Aid in Fibroid Reduction

Be sure to check with your doctor before introducing new supplements. Discuss if any of these supplements below, which have a strong reputation for creating better hormone balance, might be helpful for you:

- **Vitex (400 milligrams, 2 times daily)**. Vitex or chasteberry reduces estrogen levels by promoting the production of progesterone. For best results, vitex should be taken for at least six months.

- **Fish Oil (1,000 milligrams daily) or Flaxseed Oil (1 tablespoon daily)**. The essential fatty acids found in fish oil and flaxseed oil can help reduce inflammation in your body, which may play a part in fibroid growth.

- **B-complex (50 milligrams daily)**. If B vitamins are lacking in the diet, the liver is missing some of the raw materials it needs to carry out its metabolic processes and regulate estrogen levels.

- **Progesterone Cream (1/4 teaspoon, days 6–26 of cycle)**. Applying progesterone cream topically can help balance out low progesterone. When treating fibroids, it’s important to work with a doctor who has tested your hormone levels so you can be best advised if natural progesterone cream is the right option for your body.
THE LANDSCAPE

OPTIONS

Medical
- Symptom Management
- Targeted Therapy

Interventional

Surgery
- Myomectomy
- Hysterectomy
Medical

Symptoms
  - Tranexamic Acid
  - Hormonal Suppression

Targeted Therapy
  - SPRMs
  - GnRH Analogues
Indicated therapies

- SPRMs
- GnRH analogues
REPRODUCTIVE HORMONAL PATHWAYS

• GnRH antagonist (Oral)
• Aromatase Inhibitors

• Selective Estrogen Receptor Modulators
• Selective Progesterone Receptor Modulators

EGCG – epigallocatechin-3-gallate
Alternative Oral Agents in Prophylaxis and Therapy of Uterine Fibroids—An Up-to-Date Review

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WHAT’S BEING STUDIED

• Clinical Trials.GOV – Search “Uterine Fibroids”
• 248 studies
  • 118 drug trials
    • 21 terminated or withdrawn
    • 61 completed studies
    • 36 recruiting or may recruit
  • 70 Procedure Trials
    • 26 recruiting or may recruit
  • 65 Device Trials
VITAMIN D & ANALOGS

Why?
• Vitamin D deficiency is more common among African Americans and those with fibroids

How?
• Vit D induces apoptosis
• Paricalcitol inhibitory effect on ECM
• Reduces inflammation and fibrosis

What?
• Very early studies on cell culture lines

Does it Work? | Is it Ready?
--- | ---
Maybe | NO
DIRECT INJECTION

9 patients injected with collagenase
- Hysterectomy in all
**DIRECT INJECTION**

Jayes, Liu, Moutos, Kuchibhatla, Guilak, Leppert et al. Loss of stiffness in collagen-rich uterine fibroids after digestion with purified collagenase Clostridium histolyticum. AJOG. Nov 2016

An Open Label, Dose Escalation Study to Assess Safety and Tolerability of Collagenase *Clostridium* Histolyticum (EN3835) in Subjects With Uterine Leiomyoma (Fibroids)

- Premise: bulk of fibroid tumours are due to deposition of excessive ECM (interstitial collagen)

- Target: bulk ECM

- What: *Clostridium histolyticum* can digest interstitial collagens
  - Used in Dupuytren’s cords and Peyronie’s

- Test: post hysterectomy samples (n=17), 96 hours

- Outcomes: Highly effective at digestion of collagen = Decreased stiffness
A Pilot Study of Collagenase *Clostridium Histolyticum* as Treatment for Uterine Leiomyoma: Initial Report

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VILAPRISAN

- Large global development effort with multiple RCTs by Bayer Pharma

- Largest uterine fibroid research program globally

- ASTEROID
  Assess Safety and efficacy of Vilaprisan in subjects with uTERine fibrOIDs

- 8 total study designs
  - 2 Phase II
  - 6 Phase III
ASTEROID 1 STUDY DESIGN

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study

Screening (Up to 90 days)    Treatment (12 weeks)    Follow-up period (24 weeks)

Informed consent  Randomization (N=309*)  EoT  End of follow-up

- Women, 18–50 years old
- Uterine fibroids at screening
- ≥1 uterine fibroid with largest diameter ≥3 cm and ≤10 cm
- HMB >80 mL during the bleeding episode following screening

Primary objective
- To assess the dose–response relationship of vilaprisan in subjects with uterine fibroids

Primary endpoint
- The presence of amenorrhea

Placebo (n=58)
- VPR 0.5 mg (n=60)
- VPR 1.0 mg (n=61)
- VPR 2.0 mg (n=61)
- VPR 4.0 mg (n=60)

*Nine randomized patients dropped out of the study before receiving any study medication, full analysis set includes 300 patients.

EoT, end of treatment; HMB, heavy menstrual bleeding; VPR, vilaprisan.

Presented at SEUD 2017, Singapore
Conducted in 98 study sites across 12 countries:

EU:
- Belgium
- Bulgaria
- Czech Republic
- Finland
- Germany
- Hungary
- Spain
- Sweden

Canada

USA

Japan

Presented at SEUD 2017, Singapore
HEAVY MENSTRUAL BLEEDING STOPS DURING TREATMENT AND RETURNS DURING FOLLOW-UP

Menstrual blood loss in mL with the alkaline hematin method before, during and after treatment. EoT, end of treatment; VPR, vilaprisan.

Presented at SEUD 2017, Singapore
AMENORRHEA ACHIEVED BY DAY 6 AND MAINTAINED DURING TREATMENT

At doses ≥1 mg:
- Amenorrhea (<2 mL/28 days) was achieved within 6 days in the majority of patients
- 87–92% of patients achieved ‘amenorrhea’ by the end of the treatment course

Presented at SEUD 2017, Singapore
• Vilaprisan treatment provides effective bleeding control
• Vilaprisan effectively reduces the size of uterine fibroids
• Vilaprisan effectively relieves fibroid symptoms and improves patients’ quality of life
• No safety concerns were identified in the monitoring of general safety, endometrial safety, laboratory values and ultrasound examinations
PHASE 3 STUDIES

ASTEROID 3, 4, 7: Efficacy of VPR at 3 and/or 6 months vs. PLACEBO

ASTEROID 5: Non-inferiority Study - Efficacy VPR at 3 and/or 9 months versus UPA

ASTEROID 5 & 6: VPR up to 2 years vs UPA and non hormonal medical treatment, resp

ASTEROID 8: VPR at 3 and/or 6 months with 1 year post safety monitoring
VILAPRISAN REGIMENS

Figure 2. Vilaprisan treatment regimens

3:1 regimen
- Vilaprisan 2 mg
- 12 weeks
- Variable
- 12 weeks
- Variable
- 12 weeks
- Variable
- 12 weeks

6:2 regimen
- Vilaprisan 2 mg
- 24 weeks
- Variable
- 24 weeks
- Variable

- menstrual bleeding

- Two optimized VPR regimens will be investigated in these trials
  - A 3/1 VPR regimen – 3 months’ continuous treatment with a break of one menstrual bleed
  - A 6/2 regimen – 6 months’ continuous treatment with a break of two bleeds
ASTEROID 5 (treatment up to 2 years)

BL Vilaprisan 2 mg Vilaprisan 2 mg Vilaprisan 2 mg Vilaprisan 2 mg Vilaprisan 2 mg
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SUMMARY

• Early development options exist

• The main therapies being studied are hormonal options

• Now… for my colleagues
SEUD CONGRESS 2019

5th Congress
Of The Society of Endometriosis
And Uterine Disorders

May 16-18
Montreal, Canada

Uterine Bleeding and Fibroids:
From Bench to Bedside

Location: Hotel Bonaventure Montreal, Montreal, Canada
Congress President: Pr Philippe Laberge, Canada
SEUD President: Pr Felice Petraglia, Italy

www.seud.org
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REFERENCES


• Jayes, Liu, Moutos, Kuchibhatla, Guilak, Leppert et al. Loss of stiffness in collagen-rich uterine fibroids after digestion with purified collogenanse Clostridium histolyticum. AJOG. Nov 2016