Table 1. Evolution in Biochemical Indices in PHPT During a 15-Year Period

Variable	Baseline (n = 49)	5 Years (n = 25)	10 Years (n = 11)	13 Years (n = 9)	15 Years (n = 6)
Calcium	10.5 ± 0.1	10.7 ± 0.1	10.8 ± 0.2	11.0 ± 0.2[a]	11.1 ± 0.2[a]
PTH	122 ± 10	119 ± 12	123 ± 14	124 ± 16	121 ± 18
Urinary calcium	238 ± 19	215 ± 23	185 ± 32	247 ± 36	202 ± 36
25-OHD	21 ± 1	22 ± 2	22 ± 3	21 ± 3	19 ± 4
1,25-OH_2 D	56 ± 2	58 ± 3	54 ± 5	40 ± 5[a]	48 ± 7

1,25-OH_2D=1,25-OH vitamin D; 25-OHD=25-OH vitamin D; PTH=parathyroid hormone; PHPT=primary hyperparathyroidism.

[a] $p < .01$

Adapted from Rubin MR et al. *J Clin Endocrinol Metab*. September 2008.

serum calcium and PTH, and it had a neutral effect on BMD [Peacock M et al. *J Clin Endocrinol Metab* 2005]. Cinacalcet plus a bisphosphonate were shown to lower serum calcium and PTH, and to increase BMD [Faggiano A et al. *Endocrine* 2011].

The 2014 Guidelines recommend monitoring of serum calcium annually, as the 2009 Guidelines did [Bilezikian JP et al. *J Clin Endocrinol Metab* 2009]. The skeletal assessment with DXA every 1 or 2 y is also unchanged, but with the addition of computed tomography or VFA if clinically indicated; renal creatinine clearance assessment is still recommended annually, with the addition of a stone risk profile or abdominal imaging if clinically indicated.

Dr. Bilezikian stated that although the balance of evidence is leaning toward surgery as being the best option for patients with asymptomatic PHPT, both surgical and medical management should be considered for every patient.

Tissue-Selective Estrogen Complex: New Estrogen Receptor–Targeted Therapy

Written by Mary Mosley

The tissue-selective estrogen complex (TSEC) is a strategy to harness the benefits of estrogens while limiting their negative consequences, by combining an estrogen with a selective estrogen receptor modulator (SERM). Carolyn Smith, MD, Baylor College of Medicine, Houston, Texas, USA, reviewed research with this new class of estrogen receptor (ER)-targeted therapy.

Estrogen research is uncovering new concepts about its effects in different target tissues, and in the process it is clarifying the benefits of hormone replacement therapy, which can delay or improve many of the symptoms or diseases associated with menopause. The discovery of a second ER expands the potential for estrogen action.

Because current concepts of estrogen action are extraordinarily complex, stated Dr. Smith, this translates clinically into a variety of actions, many of which are beneficial, in diverse tissues. Estrogen is a key hormone in maintaining skeletal integrity; improved cognition and protection against tooth loss and macular degeneration are also emerging as possible benefits of estrogen.

The United States Food and Drug Administration has approved one TSEC, comprising conjugated estrogens (CE; 0.45 mg) and bazedoxifene (BAZ; 20 mg), as a treatment for moderate-to-severe vasomotor symptoms (VMS) associated with menopause and for the prevention of postmenopausal (PM) osteoporosis in women with a uterus. The estrogenic component provides relief of hot flashes and prevents bone loss, whereas the antiestrogenic component inhibits action in breast and endometrial tissue.

Basic science research has shown differential regulation of ER–target gene expression in relation to the specific SERM that was combined with CE in the TSEC [Chang KCN et al. *J Steroid Biochem Mol Biol* 2010]. TSEC activates the transcriptional activity of ER–heteroligand dimers, in which 1 receptor is bound to an agonist (CE or estradiol), and the other receptor is bound to an antagonist (tamoxifen, raloxifene, or BAZ). This activation has been shown in multiple cell types and requires both receptors to bind to DNA. TSEC stimulation of

Table 1. Design and Primary Outcomes of the SMART Trials

	SMART-I	SMART-2	SMART-3	SMART-4	SMART-5
N	3397	332	664	1083	1843
Participants	Generally healthy postmenopausal women aged 40–75 years with a uterus	Postmenopausal women aged 40–65 years with a uterus and ≥7 moderate to severe hot flashes daily or 50 per week at screening	Postmenopausal women aged 40–65 years with a uterus and moderate to severe VVA	Generally healthy postmenopausal women aged 40–65 years with a uterus	Postmenopausal women aged 40–65 years with a uterus who were seeking treatment for menopausal symptoms
Study duration	2 years	12 weeks	12 weeks	1 year + 1 year extension	1 year
Treatments, mg	CE 0.45/BAZ 10 CE 0.45/BAZ 20 CE 0.45/BAZ 40 CE 0.625/BAZ 10 CE 0.625/BAZ 20 CE 0.625/BAZ 40 Raloxifene 60 PBO	CE 0.45/BAZ 20 CE 0.625/BAZ 20 PBO	CE 0.45/BAZ 20 CE 0.625/BAZ 20 BAZ 20 PBO	CE 0.45/BAZ 20 CE 0.625/BAZ 20 CE 0.45/MPA 1.5 PBO	CE 0.45/BAZ 20 CE 0.625/BAZ 20 BAZ 20 CE 0.45/MPA 1.5 PBO
Primary end point	Incidence of endometrial hyperplasia	Frequency and severity of hot flashes	VVA measures	Incidence of endometrial hyperplasia, and change in lumbar spine BMD	Incidence of endometrial hyperplasia, and percentage change in lumbar spine BMD

BAZ=bazedoxifene; BMD=bone mineral density; CE=conjugated estrogens; MPA=medroxyprogesterone acetate; SMART=Selective Estrogens, Menopause, and Response to Therapy; PBO=placebo; VVA=vulvar-vaginal atrophy.

Reproduced from Komm BS et al. Development of conjugated estrogens/bazedoxifene, the first tissue selective estrogen complex (TSEC) for management of menopausal hot flashes and postmenopausal bone loss. *Steroids* 2014; http://dx.doi.org/10.1016/j.steroids.2014.06.004. With permission from Elsevier.

messenger RNA expression was gene specific, and it has been shown that different subsets are regulated by different combinations of agonist and antagonist [Chang KCN et al. *J Steroid Biochem Mol Biol* 2010]. Expression of ERs in breast and endometrial cells was downregulated with BAZ [Wardell SE et al. *Clin Cancer Res* 2013]. A program of 5 randomized, double-blind, placebo- and active-controlled Phase 3 trials called the Selective Estrogens, Menopause, and Response to Therapy [SMART; Komm BS et al. *Steroids* 2014] trials evaluated the safety and efficacy of the CE–BAZ TSEC in PM women with a uterus (Table 1). Together, the trials showed that this TSEC relieved VMS and vulvar-vaginal atrophy (VVA) symptoms, increased bone mineral density, exerted minimal breast stimulation, and provided adequate endometrial protection.

The preclinical work and evidence from the SMART trials support the ability of TSECs to blend the desirable ER agonist activity of estrogens and the tissue-selective ER agonist and ER antagonist properties of a SERM, stated Dr. Smith.