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A REVIEW OF INTRANASAL CORTICOSTEROIDS IN THE TREATMENT OF ALLERGIC RHINITIS

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Allergic rhinitis (AR) makes up approximately 50-60% of all rhinitis cases and it affects 30-60 million people in the United States annually. The overall costs of treating allergic rhinitis in the United States in 2005 were estimated at $11.2 billion. In 2000, it was nearly half of that at $6.1 billion (expressed in 2005 dollars). There are also indirect costs associated with AR such as days off work and poor productivity.[1] The Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Practice Parameters defines rhinitis as "a condition characterized by one or more of the following nasal symptoms: congestion, rhinorrhea (anterior or posterior), sneezing and itching." [2] In AR, these symptoms are caused by an IgE mediated inflammatory response and are assisted by inflammatory mediators such as histamine and cysteinyl leukotrienes. AR can be further subdivided by symptoms and severity. Intermittent AR has symptoms that last for < 4 days/week or for < 4 consecutive weeks while persistent AR has symptoms that last for > 4 days/week and for > 4 consecutive weeks. Some sources also refer to AR as either seasonal AR (SAR) or perennial AR (PAR). In SAR, symptoms are associated with a specific pollen season whereas in PAR, symptoms are associated with indoor allergens and can occur for a majority of the year. Mild AR has symptoms that do not interfere with sleep or daily activities whereas in moderate/severe AR, symptoms do impair sleep and daily activities.[2]

Intranasal corticosteroids (INC) are one of the options used to treat AR symptoms. They work by reducing nasal inflammation and nasal hypersensitivity. They are considered first line therapy in the treatment of moderate-severe intermittent AR or in any intensity of persistent AR.[2] The INCs currently available in the United States include beclomethasone dipropionate (BDP), budesnoide (BANS), ciclesonide (CIC), flunisolide (FLU), fluticasone furoate (FF), fluticasone propionate (FLP), mometasone furoate (MFNS) and triamcinolone acetonide (TANS). **Table 1** provides a summary of all the INCs currently available in the United States.[3-11] The objective of this review is to examine the primary literature on all intranasal corticosteroids currently available in the United States and to highlight the differences or unique properties between them; only trials with an active comparator will be summarized.

CLINICAL TRIALS

Beclomethasone (BDP)

Pullerits et al.[12] compared BDP to zafirlukast in a double-blind, double-dummy, randomized trial (n=33) (**Table 2**). All patients had a history (of at least 2 years) of AR during the grass pollen season. After nasal biopsy, patients were randomized to either BDP (50 mcg/actuation) twice in each nostril twice a day (BID) (total dose=400 mcg daily), zafirlukast (Accolate® 20 mg) BID or a matching placebo tablet / nasal spray. Treatment was started 3 weeks prior to the expected beginning of the grass pollen season and

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Table 1 | Summary of intranasal corticosteroids

Medication	Dosing and administration**	Cost/ bottle ($) *	Actuations**	Cost/ actuation ($)	Cost/ month ($)***
Beclomethasone (*Beconase*®), 25g bottle	SAR/PAR (12yrs+): 1-2 nasal inhalations in each nostril BID SAR/PAR (6-12yrs): 1 nasal inhalation in each nostril BID	204.99	180	1.14	137.34-273.32
Beclomethasone (Qnasl), 8.7g bottle	SAR/PAR (12yrs+): 2 nasal aerosol sprays in each nostril QD	152.99	120	1.27	152.99
Budesonide (*Rhinocort*®), 8.6g bottle	SAR/PAR (6yrs+): 1 spray in each nostril QD	116.99	120	0.97	58.50
Ciclesonide (*Omnaris*®), 12.5g bottle	SAR (6yrs+): 2 sprays per nostril QD PAR (12yrs+): 2 sprays per nostril QD	149.99	120	1.25	149.99
Flunisolide, 25mL bottle	SAR/PAR (14yrs+): 2 sprays in each nostril BID SAR/PAR (6-14 yrs): 1 spray in each nostril TID	50.99	200	0.25	61.19
Fluticasone Furoate (*Veramyst*®), 10g bottle	SAR/PAR (12yrs +): 2 sprays in each nostril QD SAR/PAR (2-11yrs): 1 spray in each nostril QD	144.99	120	1.21	144.99
Fluticasone Propionate (*Flonase*®), 16g bottle	SAR/PAR (adults): 2 sprays in each nostril QD SAR/PAR (children 4yrs+ & adolescents): 1 spray in each nostril QD	61.99	120	0.52	61.99
Mometasone Furoate (*Nasonex*®), 17g bottle	SAR/PAR (12yrs+): 2 sprays in each nostril QD SAR/PAR (2-11yrs): 1 spray in each nostril QD	156.99	120	1.31	156.99
Triamcinolone Acetonide (*Nasacort*®), 16.5g bottle	SAR/PAR (12yrs+): 2 sprays in each nostril QD SAR/PAR (2-12yrs): 1 spray in each nostril QD	94.99	120	0.79	94.99

BID=twice a day; PAR=perennial allergic rhinitis; QD=once a day; SAR=seasonal allergic rhinitis; TID=three times a day
*Cost/bottle was obtained from a community pharmacy in Gainesville. Prices are for an uninsured patient.
**Starting administration and actuations were obtained from respective package inserts[3-11]
***Cost/month was calculated using the number of sprays an adult patient would need per month.

patients were told to administer all drugs 1-2 hours before meals. Patients recorded their daily symptoms for sneezing, rhinorrhea, nasal itch and blockage on a scale of 0-4 (0=symptoms not present, 1=symptoms present, no discomfort, 2=some discomfort, 3=marked discomfort, no interference with activities, 4=interference with daily activities). Patients were allowed to use a short-acting antihistamine for symptom relief and cromolyn eye drops for controlling eye symptoms, but use of an antihistamine resulted in 3 points being added to the patient's symptom score scale. Each symptom got an individual score and were added together to get a total symptom score. The total symptom score was square-rooted for data analysis. Nasal biopsies were performed one month prior to the start of treatment and 6 weeks after the start of treatment to determine the degree of inflammation (measure by local tissue eosinophilia (EG2+)) at baseline and after treatment.[12]

The square-rooted total symptom score was 8.70±0.96 for placebo, 8.21±1.09 for zafirlukast, and 3.90±1.24 for BDP. Symptom scores for BDP were significantly different from placebo (p=0.005) and zafirlukast (p=0.01). The delta changes in EG2+ for the treatment groups were as follows: 190.5±75.1 for placebo, 115.8±52.6 for zafirlukast and 23.2±39.4 for BDP. The increase in EG2+ was significantly lower for BDP compared to placebo (p=0.015), but was not significantly different when BDP was compared to zafirlukast (p=0.08). The authors concluded that INCs are more effective than leukotriene antagonists at relieving symptoms of SAR, but both are effective at preventing the signs of inflammation. However, even though the change in EG2+cells was not significantly different between zafirlukast and BDP, the magnitude of the increase was less for BDP than for zafirlukast. One potential limitation of this study was that the effects of both interventions could have been blunted

Table 2 | Summary of intranasal corticosteroids trials

Study	Intervention	Results
Pullerits et. al. (1999)[12]	BDP 50µg twice in each nostril BID Zafirlukast 20mg caps BID PL	Square-rooted total symptom score: 8.70±0.96 for PL, 8.21±1.09 for zafirlukast, 3.90±1.24 for BDP Δ in EG2+ (cells/mm^2): 190.5±75.1 for PL, 115.8±52.6 for zafirlukast, 23.2±39.4 for BDP -Sx score for BDP was different from PL (p=0.005) and zafirlukast (p=0.01) -The ↑ in EG2+ was ↓ for BDP vs. PL (p=0.015), but not different for BDP vs. to zafirlukast (p=0.08)
Sahay et. al. (1980)[13]	FLU two actuations (25µg/act) into each nostril BID (total: 200µg) BDP one actuation (50µg/act) in each nostril QID (total: 400 µg)	Mean symptoms scores: FLU: sneezing (-1.44±0.75), stuffiness (-1.74±0.76), runny nose (-1.33±1.07), nose blowing (-1.70±0.91). BDP: sneezing (-1.57±0.68), stuffiness (-1.62±0.98), runny nose (-1.48±1.02) nose blowing (-1.72±0.84) FLU and BDP effective vs. sneezing, stuffiness, runny nose and nose blowing (P<0.001)
Takahashi et. al. (2012)[14]	FLP (50 mcg) per nostril BID (total dose: 200 mcg/day) & FEX 60 mg BIDfor exacerbations FEX 60 mg BID & FLP (200 mcg/day) for exacerbations	Median area under the TNSS curve: FLP: 45 (IQR: 25 to 75), FEX: 109 (IQR: 75 to 158) (p=0.0015) No significant difference between FLP and FEX for the median area under the TOSS curve (p=0.8358)
Varshney et. al. (2012)[15]	FLP two sprays in each nostril (total dose=200mcg) CIC two sprays in each nostril (total dose 200 mcg) 30 min before cross-over	FLP more soothing feel (p<0.001), more satisfying scent (p<0.001) and decreased nasal irritation (p=0.002) TNSS: CIC: decreased from 8 (IQR: 7-9) to 3 (IQR: 2-4), FLP: decreased from 8 (IQR 6-10) to 2 (IQR 2-4) (FLP =CIC in reducing symptoms)
Mandl et. al. (1997)[16]	MFNS 200 mcg QD FLP 200 mcg QD PL	Mean percent reduction in combined morning and evening TNSS (from baseline): MFNS: 37% to 63%, FLP: 39% to 60%, PL: 22% to 39% MFNS and FLP were both significantly more effective than PL (p<0.01), but MFNS was not statistically different from FLP (p≥0.43)
Day et. al. (1998)[17]	BANS (64 mcg/spray) 2 sprays in each nostril qAM x 6 wks FLP (50 mcg/spray) 2 sprays in each nostril qAM x 6 wks PL	Mean nasal symptom score reduction: BANS: 2.11, FLP: 1.65 BANS had better reduction vs. FLP (p=0.031). Onset of action: BANS showed significant change vs. PL in 36 hrs (p=0.012) FLP showed significant change vs. PL in 60 hrs (p<0.001)
Schoenwetter et. al. (1995)[19]	TANS two sprays (55 mcg/act) per each nostril QD and 1 PL cap Loratidine 10 mg tab QD and PL nasal spray	Mean change in TNSS: TANS: -5.02±3.20, Loratadine: -2.96±2.68 Mean change in ocular symptom score: TNSS: -0.80±0.78, Loratadine: -0.69±0.69 The TANS group had better improvements in all allergic symptoms except ocular symptoms (p≤0.01)

Δ=Change, BID=twice a day; CI-confidence interval; FEX=fexofenadine; hrs=hours; IQR=Interquartile Range; PL=Placebo; qAM=in the morning; QD=once a day; QID=four times a day; qPM=in the evening; TNSS=total nasal symptom score; TOSS=total ocular symptom score

because the study area (Finland) is generally recognized as having lower grass pollen levels compared to warmer climates like central Europe and Great Britain. However, the grass pollen season for the study area was considered as an average severity.[12]

Qnasl® is a dry intranasal aerosol formulation of BDP; while it does utilize a unique method of administration, there have been no clinical trials to determine how effective it is in AR compared to an aqueous formulation of BDP.

Flunisolide (FLU)

Sahay et. al. performed a randomized, open, parallel comparison between FLU and BDP (n=56).[13] All participants suffered from PAR with or without SAR. Patients were allowed to remain on steroid inhalers for asthma if they were stable and remained stable during the trial. Patients were randomized to FLU (25 mcg/actuation), two actuations into each nostril BID (total dose 200 mcg), or BDP (50 mcg/actuation), one actuation into each nostril four times a day (QID) (total dose 400 mcg). Patients used their medication for 4 weeks and were assessed on admission to the study and after the 4 weeks. Sneezing, stuffiness, runny nose, nose blowing, post-nasal drip and epistaxis were all assessed on a scale of 0-3; participants were also asked if symptoms interfered with their daily activities or sleep. After 4 weeks, FLU resulted in a mean reduction in symptom scores for the following: sneezing, (-1.44±0.75); stuffiness, (-1.74±0.76); runny nose, (-1.33±1.07); and nose blowing, (-1.70±0.91). For BDP the mean reduction in symptom scores was: sneezing, (-1.57±0.68); stuffiness, (-1.62±0.98); runny nose, (-1.48±1.02); and nose blowing, (-1.72±0.84). The authors concluded that FLU and BDP were both effective at treating sneezing, stuffiness, runny nose and nose blowing (P<0.001). This study supports the assumption that all INCs are equally effective for treating allergic rhinitis symptoms, if used in equivalent doses. A potential limitation of this study was the administration of FLU and BDP. Even though the number of sprays per day was the same, FLU was given as two sprays BID while BDP was given as one spray QID. Since BDP had to be taken QID, adherence may be a potential disadvantage.[13]

Fluticasone Propionate (FLP)

Takahashi et. al. compared initial treatment of FLP with initial treatment of fexofenadine hydrochloride tablets (FEX) in a randomized, open-label, parallel group trial (n=51).[14] Patients were at least 16 years old, had a history of Japanese cedar pollinosis (for at least 2 seasons), had a positive allergy skin test to Japanese cedar pollen and were asymptomatic or had mild symptoms before the pollen season began (daily total nasal symptom score [TNSS] ≤ 2). If a patient qualified, they were randomized to either FLP 50 mcg per nostril BID plus FEX 60 mg BID for treating exacerbations or FEX 60 mg BID plus FLP 50 mcg per nostril BID for treating exacerbations. Both groups were allowed to use sodium cromoglicate 2% eye drops for relief of ocular symptoms. On a daily basis, patients were asked to assess 4 nasal symptoms (runny nose, stuffy nose, sneezing and itchy nose) and 3 ocular symptoms (tearing, redness and itchy eyes) on a 4 point Likert scale. The authors graphed the median TNSS and median total ocular symptom score (TOSS) for the pollen season (January 19, 2007 to March 23, 2007) and used the area under the curve (AUC) to compare the two groups.[14]

The median TNSS AUC for FLP was 45 (Interquartile range (IQR): 25 to 75) while the median TNSS AUC for FEX was 109 (IQR: 75-158). The AUC of the FLP group was significantly different from the AUC of the FEX group (p=0.0015). However, in terms of the AUC for the TOSS, the two intervention groups were not significantly different (p=0.8358). The authors concluded that FLP used as the initial treatment was more effective than FEX used as the initial treatment in SAR. A potential limitation of this study was that the small sample size could have decreased the statistical power of this study. However, the authors believe that this is unlikely due to the large difference that was seen between the FLP group and the FEX group.[14]

Varshney et al. compared FLP to CIC in terms of sensory attributes (scent, taste, aftertaste, soothing feel, etc.).[15] The study was a randomized, double blind, single dose, crossover study (n=74). All participants were 12 years of age or older, had symptoms of allergic rhinitis for at least 1 year and had a TNSS of six or more (with an individual score of 2 or more for rhinorrhea or nasal congestion). Patients were randomized to FLP (2 sprays in each nostril, total dose=200 mcg) and then CIC (2 sprays in each nostril, total dose=200mcg) or vice-versa. A 30 minute interval separated the two administrations and a washout protocol was started 10 minutes before administration of either nasal spray (both nasal sprays were administered on the same day). Sensory attributes were evaluated with 13 questions on a 7 point Likert scale, while immediate efficacy was assessed by TNSS. A final follow-up was done by telephone 24 hours after administration.[15]

FLP demonstrated a more soothing feel (p<0.001), a more satisfying scent (p<0.001) and less nasal irritation (p=0.002). However, in regards to immediate efficacy, there was no difference between FLP adminis-

tered first and CIC administered first. CIC decreased TNSS from 8 (IQR: 7-9) to 3 (IQR: 2-4) while FLP decreased it from 8 (IQR 6-10) to 2 (IQR 2-4). The authors concluded that there is no difference in efficacy, when choosing between FLP and CIC, but FLP may be preferred because of more pleasing sensory attributes. A limitation of this study is that both medications were administered on the same day so there is no way to know how each medication would have controlled the patient's symptoms for the entire day.[15]

Mandl et al compared the efficacy of MFNS to FLP in a 3 month, randomized, double-blind, double dummy, parallel group study (n=550).[16] Patients had to be at least 12 years of age, have at least a 2 year history of moderate to severe PAR, have a positive skin prick test to at least one perennial allergen and have symptoms at screening and at baseline visits (a TNSS of at least 5 with a score of at least 2 for rhinorrhea and/or congestion). If a patient qualified for the study they were randomized into one of three treatment groups: MFNS 200 mcg in the morning (qAM), FLP 200 mcg qAM or a matching placebo (all medications were given as [50 mcg/actuation] 2 sprays in each nostril). Patients were asked to record their nasal symptom scores in the morning (prior to dosing) and in the evening (about 12 hours later). The mean percent reduction in combined morning and evening TNSS, compared to baseline, ranged from 37% to 63% for MFNS, 39% to 60% for FLP and 22% to 39% for placebo. MFNS and FLP were both significantly more effective than placebo ($p<0.01$), but MFNS was not statistically different from FLP ($p\geq0.43$).[16]

Day et. al. compared the efficacy of BANS to FLP in a multicenter, blinded, randomized, parallel-group, placebo-controlled trial (n=273).[17] Patients were at least 18 years of age, had at least a 1 year history of PAR, and had a positive skin prick test to 1 or more perennial allergens within 1 year of the start of the study. If a patient qualified, they would enter an 8 to 14 day baseline period where they would have to exhibit at least 2 of 3 symptoms of rhinitis (blocked nose, runny nose or sneezing) with a severity of 1 or more on a 0-3 scale for at least 8 out of the 14 days. If a patient exhibited 2 of the 3 symptoms, they were randomly assigned to either BANS (64 mcg/spray) 2 sprays in each nostril qAM for 6 weeks, FLP (50 mcg/spray) 2 sprays in each nostril qAM for 6 weeks or a matching placebo nasal spray. Every evening, patients were asked to evaluate their nasal and eye symptoms for the preceding 24 hour period on a 4-point scale.[17]

From baseline, nasal symptom scores were reduced by 2.11 for BANS compared to placebo ($p<0.001$) and by 1.65 for FLP compared to placebo ($p=0.0012$). BANS had a significantly greater reduction when compared to FLP ($p=0.031$). BANS showed a statistically significant change from placebo in 36 hours ($p=0.012$) while FLP showed a statistically significant change from placebo in 60 hours ($p<0.001$). The authors concluded that BANS was more effective and worked faster than FLP at treating nasal symptoms in PAR. However, both INCs were more effective than placebo at treating nasal symptoms. A limitation of this article was that it was not designed to determine time to onset (time intervals were designed to be in increments of 24 hrs instead of individual time points). Therefore, additional studies will have to be done in order to prove that BANS actually has a faster onset of action than FLP.[17]

Fluticasone Furoate (FF)

FF is an INC that is similar to FLP; the only difference between the two medications is that FF has a furoate ester attached to the 17α-OH group while FLP has a propionic acid group attached. FF has a higher binding affinity for the glucocorticoid receptor compared to FLP and MFNS, but it is still questionable if these differences are clinically relevant.[18] Currently, there have been no trials that directly compare the efficacy of FLP to FF.

Triamcinolone Acetonide (TANS)

Schoenwetter et. al. tested TANS vs. loratadine in patients with SAR.[19] The study was a multicenter, double-blind, randomized, controlled, parallel-group trial (n=274). Patients were between the age of 12 and 70 and in otherwise good health, except for the diagnosis of SAR. Patients had to have a SAR history of at least two consecutive seasons characterized by nasal congestions, rhinorrhea, postnasal drip, sneezing and nasal itch with or without eye symptoms and verification with a positive skin test to ragweed. After that, patients entered a baseline period of up to 28 days and were given diaries and told to record their rhinitis symptoms on a 4 point scale. Any patient that had at least 5 consecutive days of a TNSS of 24 or more was randomly placed into a group that received either 28 days of TANS 220 mcg (two sprays of 55 mcg/actuation in each nostril) and 1 placebo capsule or 28 days of a placebo nasal spray and 1 loratadine 10 mg tablet. The mean change in TNSS was -5.02±3.20 for TANS and -2.96±2.68 for loratadine ($p\leq0.001$). However, for the ocular symptom score, TANS had a mean change of -0.80±0.78 while loratadine had a mean change of -0.69±0.69 (not statistically significant, $p>0.01$). The authors concluded that the TANS group had greater improvements in all allergic symptoms except ocular symptoms ($p\leq0.01$).[19]

SUMMARY

Some clinical trials suggest that INCs have similar efficacy,[13,15,16] while others show that INCs are more effective than second generation oral antihistamines[14,19] or leukotriene receptor antagonists.[12] BANS is the only INC available that has a pregnancy category B [20] and was proven to be more effective than FLP at relieving PAR symptoms.[17] While FLP and CIC showed similar efficacy, FLP had more pleasing sensory attributes and was preferred over CIC.[15] FLU is currently the least expensive nasal spray at $0.25/actuation, but BANS is cheaper on a monthly basis ($58.50/month). FLU and BDP require BID dosing whereas most of the other INCs can be given QD. In terms of efficacy and price per month, BANS appears to be the best option, but all INCs have been shown to be effective at treating AR symptoms.[2,17]

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OSPEMIFENE: A SERM FOR THE TREATMENT OF POSTMENOPAUSAL DYSPAREUNIA

Sarah McNeill, Pharm.D. Candidate

One of the problems most frequently reported by postmenopausal women is dyspareunia, or painful sexual intercourse.[1] Dyspareunia is a symptom of vulvovaginal atrophy (VVA), caused by decreased estrogen levels. VVA is reported by 25-50% of postmenopausal women.[2] Women with VVA may experience physical discomfort, sexual dysfunction, emotional distress, and reduced quality of life.[3]

Ospemifene (Osphena®) is a new selective estrogen receptor modulator (SERM) indicated for the treatment of moderate to severe dyspareunia. Ospem-

Table 1 | Pharmacokinetics of ospemifene [6]

Property	Ospemifene
Time to peak concentration	2.5 hours
Volume of distribution	448 L
Elimination half-life	26 hours
Protein binding	>99%
Metabolism	CYP3A4, CYP2C9, and CYP 2C19
Excretion	75% fecal 7% urine

CYP=cytochrome P450 enzymes, L=liters

ifene is marketed by Shionogi, Inc. and received FDA approval in February of 2013. This article will review the pharmacology, pharmacokinetics, clinical trial data, and administration of ospemifene.

Pharmacology & Pharmacokinetics

Ospemifene is a SERM. Estrogen receptors are found in genitourinary, uterine, breast, and bone tissues.[4] SERMs act as estrogen agonists in some tissues and antagonists in others. Ospemifene has agonist activity in the vagina and antagonist activity on endometrial and breast tissue.[5]

After a single oral dose with a high fat meal, plasma concentrations reached their peak in approximately 2.5 hours (**Table 1**). Bioavailability of ospemifene is increased by 2-3 fold when taken with food. Steady state concentrations were reached after nine days. Ospemifene is primarily metabolized by cytochrome P450 enzymes such as CYP3A4, CYP2C9, and CYP2C19. This leads to the possibility of drug-drug interactions with drugs that induce or inhibit these CYP enzymes.[6]

Clinical Trials

The safety and efficacy of ospemifene was studied in three placebo-controlled clinical trials (Table 2).

The first clinical trial was a 12-week, randomized, double-blind, placebo-controlled, parallel-group study of ospemifene in 826 postmenopausal women who had 5% or less superficial cells on a vaginal smear, vaginal pH greater than 5.0, and at least one moderate to severe symptom of VVA.[7] Participants were randomized to receive ospemifene 30 mg once daily, ospemifene 60 mg once daily, or placebo. Primary endpoints were percentage of superficial cells on the vaginal smear, percentage of parabasal cells on the vaginal smear, vaginal pH, and self-assessed most bothersome moderate to severe symptom (MBS) of vaginal dryness or dyspareunia.

Both doses of ospemifene showed statistically significant improvement in the symptom score for participants reporting a MBS of vaginal dryness when compared with placebo. The score was reduced by 1.22 in the ospemifene 30 mg group (compared to placebo, p=0.04), by 1.26 in the ospemifene 60 mg group (compared to placebo, p=0.021), and by 0.84 for the placebo group. The symptom score for participants reporting a MBS of dyspareunia was decreased by 1.19 in the group receiving 60 mg of ospemifene when compared to placebo (p=0.023). The decrease of 1.02 in the group receiving 30 mg of ospemifene was not statistically significant. The percentage of superficial cells was increased by 2.2% in the placebo group, by 7.8% in the ospemifene 30 mg group, and by 10.8% in the ospemifene 60 mg group (compared to placebo, p<0.001 for both). The percentage of parabasal cells was decreased by 3.98% in the placebo group, by 21.9% in the ospemifene 30 mg group, and by 30.1% in the ospemifene 60 mg group. The decrease in vaginal pH was 0.10 in the placebo group, 0.67 in the ospemifene 30 mg group, and 1.01 in the ospemifene 60 mg group (compared to placebo, p<0.001 for both). The most common side effects were hot flashes, urinary tract infections, and headache.[7]

The second clinical trial was a 12 week, randomized, double-blind, placebo-controlled, study that enrolled 605 postmenopausal women who identified dyspareunia as their MBS and has a diagnosis of VVA.[4] Participants were randomized to receive ospemifene 60 mg once daily or placebo. Primary endpoints were similar to the previous trial by Bachmann et al.[7] The percentage of parabasal cells was not changed in the placebo group and was decreased by 40.2% in the ospemifene group (p<0.0001). The percentage of superficial cells increased by 1.7% in the placebo group and by 12.3% in the ospemifene group (p<0.0001). The mean reduction in vaginal pH was 0.07 in the placebo group and 0.94 in the ospemifene group (p<0.0001). The reduction in the MBS severity score was 1.2 in the placebo group and 1.5 in the ospemifene group (p=0.0001). The most commonly reported adverse events were hot flashes, urinary tract infection, vaginal candidiasis, vaginal discharge, vulvar and vaginal mycotic infections, nasopharyngitis, and headache.[4]

A total of 180 nonhysterectomized women who successfully completed the first clinical trial by Bachmann et al. were voluntarily enrolled in a randomized, double-blind, placebo-controlled, long-term safety extension study to study the safety and tolerability of ospemifene.[5,7] Participants were randomized to receive ospemifene 30 mg, ospemifene 60 mg, or placebo for 40 weeks. Safety assessments included

Table 2 | Summary of ospemifene clinical trials [4,5,7]

Trial	Design	Intervention	Results
Trial One Bachmann et al. (2010)[7]	R, DB, PC, PG, n=826 1º outcomes: (1) Change in % of superficial cells (2) Change in % of parabasal cells (3) Change in vaginal pH (4) Change in severity of MBS	Ospemifene 30 mg, ospemifene 60 mg, or placebo	1º outcomes: (1) 30 mg: 21.9% dec, 60 mg: 30.1% dec, PL: 3.98% dec (p<0.001) (2) 30 mg: 7.8% inc, 60 mg: 10.8% inc, PL: 2.2% inc (p<0.001) (3) 30 mg: mean dec of 0.67, 60 mg: mean dec of 1.01, PL: mean dec of 0.10 (p<0.001) (4) 30 mg: NS, 60 mg: mean dec of 1.19, PL: mean dec of 0.89 (p=0.023)
Trial 2 Portman et al. (2013)[4]	R, DB, PC, n=605 1º outcomes: (1) Change in % of parabasal cells (2) Change in % of superficial cells (3) Change in vaginal pH (4) Change in severity score of dyspareunia	Ospemifene 60mg or placebo	1º outcomes: (1) Ospemifene: 40.2% dec, PL: NS (p<0.0001) (2) Ospemifene: 12.3% inc, PL: 1.7% inc (p<0.0001) (3) Ospemifene: mean dec of 0.94, PL: mean dec of 0.07 (p<0.0001) (4) Ospemifene: mean dec of 1.5, PL: mean dec of 1.2 (p=0.0001)
Long-term safety trial Simon (2012)[5]	MC, R, DB, PC, n=180 1º outcomes: Adverse changes in safety assessments (i.e. adverse events, endometrial thickness, mammography)	Ospemifene 60 mg, Ospemifene 30 mg, or placebo	No clinically significant adverse changes in safety assessments in any treatment group

Legend: DB=double-blind, dec=decrease, inc=increase, MC=multicenter, NS= no significant change, PC=placebo controlled, PG= parallel group, MC=multicenter, R=randomized

adverse events, cervical Papanicolaou tests, endometrial histology, endometrial thickness, gynecological examination, breast palpation, mammography, physical examination, and clinical safety laboratory assessments. No clinically significant adverse changes in safety assessments were observed in any group. The number of participants that discontinued the trial due to adverse events was 1 in the placebo group, 3 in the ospemifene 30 mg group, and 4 in the ospemifene 60 mg group. A slight increase in mean endometrial thickness was seen in both ospemifene groups. The change from baseline was -0.04 mm for the placebo group, 0.68 mm for the ospemifene 30 mg group, and 1.14 mm for the ospemifene 60 mg group. No cases of endometrial hyperplasia or carcinoma were observed. Breast palpations were normal in all but one participant in the ospemifene 60 mg group. Mammograms were normal in all but one participant in the ospemifene 60 mg group, which resolved by the end of the study.There were small changes in total cholesterol, LDL cholesterol, and HDL cholesterol. The mean percentage changes from baseline for total cholesterol were -1.05 in the placebo group, -0.55 in the ospemifene 30 mg group, and -2.45 in the ospemifene 60 mg group. The mean percentage changes from baseline for LDL cholesterol were -0.42 in the placebo group, -0.87 in the ospemifene 30 mg group, and -6.20 in the ospemifene 60 mg group. The mean percentage changes from baseline for HDL cholesterol were -4.41 in the placebo group, 6.07 in the ospemifene 30 mg group, and 1.29 in the ospemifene 60 mg group Hot flushes were the most frequently reported adverse event. Hot flushes occurred in 7.2% of the ospemifene 60 mg group, 3.2% of the ospemifene 30 mg group, and in 2.0% of the placebo group. Most adverse events were mild to moderate in severity.[5]

Adverse Events and Safety

Ospemifene is generally well tolerated (Table 3). Most adverse events were mild to moderate in severity with the most commonly reported events being hot flashes, headache, and urinary tract infection.[6] In the extension study, the discontinuation rate due to adverse reactions in the ospemifene 60 mg group was 5.8%.[6]

Ospemifene is an estrogen agonist/antagonist. Unopposed estrogen can increase the risk of stroke, venous thromboembolism, and endometrial cancer. Ospemifene is contraindicated in abnormal genital bleeding, estrogen-dependent neoplasia, active or a history of deep vein thrombosis (DVT) or pulmonary embolism, and active or a history of arterial thromboembolic disease (i.e. stroke or myocardial infarction).[6]

Table 3 | Most common adverse reactions with ospemifene (60 mg daily) vs. placebo [6]

	Ospemifene 60 mg (N=1242) %	Placebo (N=958) %
Vascular Disorders: Hot flush	7.5	2.6
Reproductive System and Breast Disorders: Vaginal discharge, genital discharge	3.81.3	0.30.1
Musculoskeletal and Connective Tissue Disorders: Muscle spasms	3.2	0.9
Skin and Subcutaneous Tissue Disorders: Hyperhidrosis	1.6	0.6

Adverse events occurring at a frequency ≥1%

Drug Interactions

Ospemifene is metabolized by CYP3A4, CYP2C9, and CYP2C19. This leads to the possibility of drug-drug interactions. Fluconazole is a moderate CYP3A4, strong CYP2C9, and moderate CYP2C19 inhibitor. Fluconazole increases the systemic exposure of ospemifene and may increase the risk of adverse events. Fluconazole should not be used with ospemifene. Rifampin is a strong CYP 3A4, moderate CYP2C9, and moderate CYP2C19 inducer which decreases the systemic exposure of ospemifene by 58%. Rifampin may decrease the clinical effect of ospemifene. Ketoconazole is a strong CYP3A4 inhibitor, which increases the systemic exposure of ospemifene. Chronic administration of ospemifene with ketoconazole may increase the risk of ospemifene-related adverse reactions. Ospemifene is also more than 99% bound to serum proteins. Ospemifene combined with another highly protein bound drug may lead to increased exposure of either drug.

Dosing & Administration

The recommended dose of ospemifene is 60 mg once daily. Ospemifene should be taken with food. Dose adjustments are not necessary in patients with mild to moderate hepatic impairment or renal insufficiency. Ospemifene has not been studied in patients with severe hepatic disease; therefore use in these patients is not recommended.

Ospemifene should be used with a progestin in women with an intact uterus to reduce the risk of endometrial cancer. Ospemifene should be used for the shortest duration possible in accordance with the treatment goals of individual women.[6]

Summary

Dyspareunia due to VVA affects millions of women in the United States and is largely untreated. Ospemifene (Osphena®) is a new SERM approved by the FDA for the treatment of moderate to severe dyspareunia in postmenopausal women. Ospemifene acts as an agonist in the vagina and an antagonist in the endometrium and breast tissue. Ospemifene has been shown to significantly reduce dyspareunia when compared to placebo. The most commonly reported adverse event was hot flushes. Ospemifene 60 mg should be taken once daily with food.

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Clinical Trial Update

Duration of steroid therapy – Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with significant morbidity and mortality. Exacerbations are commonly treated with short courses of systemic corticosteroids with or without antibiotics. However, an optimal dose and duration of corticosteroid therapy has not been fully elucidated.

Leuppi and colleagues[1] designed a randomized trial to compare a short- and long-course of prednisone in those experiencing a COPD exacerbation. To be eligible, patients had to have at least two symptoms of a COPD exacerbation (change in dyspenea, cough, or sputum quality or purulence), be over the age of 40, and have a 20-year pack history of smoking or more. Key exclusion criteria included a diagnosis of asthma or pneumonia.

Patients received an initial dose of 40 mg IV methylprednisolone on day 1 followed by 4 days of open-label prednisone at a dose of 40 mg daily. Starting on day 6 patients were randomized in a blinded-fashion to either continue prednisone 40 mg daily or receive placebo until day 14; additional steroids could be administered at the discretion of the treating physician. All patients also received a 7-day course of a broad-spectrum antibiotic (agent not specified), inhaled tiotropium daily, and an inhaled corticosteroid/beta-2 agonist combination twice daily. The primary outcome was time to next COPD exacerbation during a follow-up period of 6 months.

In total 314 patients were enrolled and 155 were randomized to receive 14 days prednisone while 156 received 5 days of prednisone. Baseline characteristics did not differ significantly between groups except for a larger percent of females present in the 14-day treatment group. The average age was 69.8 years, 40% were current smokers and 60% were former smokers; approximately 85% of patients were classified as GOLD grade 3 or 4 based on spirometry.

The primary end point was reached in 56 patients (35.9%) in the 14-day treatment group compared to 57 patients (36.8%) in the 5-day treatment group; additionally the hazard ratio (HR) for exacerbations did not differ between the 5-day and 14-day treatment groups (HR 0.95, 90% confidence interval 0.70-1.29) meeting prespecified criteria for non-inferiority. No differences were noted between groups in a variety of secondary outcomes except a difference in cumulative prednisone exposure (mean exposure: 379 mg for 5-day treatment vs. 793 mg for 14-day treatment, p<0.001). There were no differences in length of hospital stay or treatment-related adverse effects.

The authors concluded that a 5-day course of prednisone is non-inferior to a 14-day course for the treatment of a COPD exacerbation. Although there was no difference between groups in adverse effects, reducing exposure to corticosteroids could produce long-term benefits and reduce overall treatment costs, especially in those with frequent exacerbations requiring systemic corticosteroid therapy.

1. Leuppi JD, et al. JAMA 2013;309:2223-31.

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