Drug Information Newsletter
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The University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS) Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals/medications under development, medication shortages, and drug class reviews.

**New Drug Therapy for Pulmonary Arterial Hypertension: Selexipag (Uptravi®)**
Caitlin Hoar, PharmD

**Introduction**

Pulmonary arterial hypertension (PAH) is a form of pulmonary hypertension resulting in high blood pressure in the arteries and lungs and is caused by a variety of conditions.1 PAH is a rare but complex progressive disease of the pulmonary vasculature that can lead to right ventricular failure and death if not treated appropriately. Pulmonary hypertension is classified by the World Health Organization (WHO) into groups (1-5) depending on etiology of the disease; WHO group 1 refers to PAH. According to data from the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL), between 2006 and 2007, the incidence of PAH in the United States was 2.3 cases per million and the prevalence was 12.4 cases per million.2 The Pulmonary Hypertension Connection registry, in combination with REVEAL, estimate the 5-year survival of patients with PAH to be approximately 60%.1 Due to the complexity of the disease, PAH may be associated with high costs and utilization of healthcare resources, with estimates of per-patient-per-month costs up to 4 to 5 times higher for PAH patients than patients without PAH matched for age, sex, geographic region, and employment status.

Selexipag (Uptravi®) was approved in December of 2015 as an oral prostacyclin receptor agonist indicated for the treatment of PAH (WHO Group 1) to delay disease progression and reduce the risk of hospitalization for PAH.3 The prostacyclin pathway is an important medical target in treatment of PAH, as prostacyclin synthase is reduced in patients...
with PAH; this results in reduced production of prostacyclin, which is a potent vasodilator with antiproliferative effects. Agonism of the prostacyclin receptors by selexipag reduces vasoconstriction and smooth muscle proliferation, translating to improvement in PAH. Other prostacyclin agonists include epoprostenol and treprostinil, which are administered intravenously, and iloprost, which is administered via inhalation. Treprostinil may also be administered subcutaneously or orally (available as an inhalation solution and extended-release tablets). Notably, there have not been any head-to-head clinical trials comparing prostacyclin agonists, and none of these 3 drugs have been shown to delay disease progression or reduce PAH hospitalization.

**Figure 1** illustrates the pathophysiology of PAH and medical targets for treatment. Other treatment options include endothelin receptor antagonists, such as ambrisentan, bosentan, and macitentan, phosphodiesterase-5 inhibitors, such as sildenafil and tadalafil, and riociguat, which stimulates soluble guanylate cyclase (sGC), thereby affecting the nitric oxide pathway.

**Figure 1. Medical therapy targets in PAH.**

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cAMP=cyclic adenosine monophosphate; cGMP=cyclic guanosine monophosphate; ERA=endothelin receptor antagonist; PAH=pulmonary arterial hypertension; PDE-5=phosphodiesterase type 5

**Clinical Pharmacology**

Selexipag is an oral selective prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed to an active metabolite, which is approximately 37 times as potent as selexipag and is also selective for the IP receptor. Activation of the IP receptor produces cyclic adenosine monophosphate, thereby inducing vascular smooth muscle relaxation and decreasing vascular pressure and pulmonary vascular resistance. This may also result in an increase in cardiac index. Per the manufacturer, selexipag does not cause QT prolongation and does not affect platelet aggregation at clinically relevant concentrations. Following oral administration, selexipag reaches maximum plasma concentrations after 1-3 hours and its metabolite after 3-4 hours. When taken with food, time to peak concentration (T_{max}) is delayed and the peak plasma concentration (C_{max}) is about 30% lower. Both selexipag and its active metabolite are highly protein-bound (99%). Selexipag is heptatically metabolized by carboxylesterase 1, and the reaction is catalyzed by cytochrome P450 (CYP) 3A4 and CYP2C8. The active metabolite then undergoes glucuronidation by uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A3 and UGT2B7. Concomitant administration with strong CYP2C8 inhibitors, such as gemfibrozil, may result in significant increases in exposure to selexipag and its active metabolite; therefore, concomitant use of these drugs should be avoided. Selexipag and its metabolite do not induce or inhibit any CYP450 enzymes. The half-life of selexipag is 0.8-2.5 hours, while the active metabolite has a half-life of 6.2-13.5 hours.
Clinical Efficacy

Approval of selexipag by the Food and Drug Administration was primarily based on findings from the Prostacyclin (PGI2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study.9 GRIPHON was an event-driven, phase 3, randomized, double-blind, placebo-controlled trial examining the safety and efficacy of selexipag in patients with PAH who were not receiving therapy at baseline and those who were receiving either an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both at baseline.10 Eligibility criteria included age between 18 and 75 years and confirmed idiopathic or heritable PAH, or PAH associated with human immunodeficiency virus infection, drug use or toxin exposure, connective tissue disease, or repaired congenital systemic-to-pulmonary shunts. Patients were also required to have a 6-minute walk distance (6MWD) of 50 to 450 meters and a pulmonary vascular resistance of ≥5 Wood units. Patients who were receiving baseline therapy for PAH were required to have stable doses for ≥3 months; patients receiving prostacyclin analogs were not eligible.

Patients were randomized in a 1:1 fashion to selexipag or placebo.10 There was a 12-week dose-adjustment phase in which selexipag was initiated at 200 mcg twice daily and increased weekly, in twice-daily increments of 200 mcg, to a maximum of 1600 mcg twice daily. Doses were increased as tolerated. If intolerable side effects occurred, doses were reduced in 200 mcg increments to maximally-tolerated amounts. After these 12 weeks, patients entered the maintenance phase of the study. Further dose increases were allowed at week 26; dose reductions were allowed at any time. Patients were assessed at weeks 8, 16, and 26, and every 6 months thereafter.

The primary endpoint was time to first event of several complications related to PAH and all-cause mortality, assessed over 26 weeks.10 Complications included disease progression, defined as ≥15% decrease from baseline in 6MWD in combination with worsening in WHO functional class (for patients with baseline WHO class of II or III), or the need for additional PAH treatment (for patients with baseline WHO class of III or IV). Other complications included in the primary composite endpoint were initiation of parenteral prostanoctid therapy or long-term oxygen therapy, the need for lung transplantation or balloon arterial septostomy, and PAH worsening that resulted in hospitalization. Secondary endpoints were change in 6MWD from baseline to week 26, absence or worsening of WHO functional class from baseline to week 26, hospitalization or death due to PAH up to study completion, and death from any cause.

A total of 1156 patients were enrolled across 181 centers in 39 different countries and underwent 1:1 randomization; 574 received selexipag and 582 received placebo.10 The median duration of therapy was 63.7 to 70.7 weeks (placebo and selexipag arms, respectively), with the end of the treatment period being 7 days after the last dose of selexipag or placebo. The majority of patients enrolled in the study were female (79.8%) and aged <65 years (82.1%, mean 48.1 years). Most patients had idiopathic PAH (56.1%) or PAH associated with connective tissue disease (28.9%) with WHO functional class of II (45.8%) or III (52.5%). Approximately 20.4% of patients were not on PAH therapy at baseline; 14.7% were using endothelin-receptor antagonists, 32.4% were using phosphodiesterase type 5 inhibitors, and 32.5% were using both agents. The mean 6MWD at baseline was 353.5 ± 76.31 m and 348.0 ± 83.23 m in the selexipag and placebo groups, respectively.

From baseline to 26 weeks, treatment with selexipag resulted in a 40% reduction in the risk of the primary composite endpoints of death or complications related to PAH (hazard ratio [HR] 0.60, 99% confidence interval [CI] 0.46 to 0.78).10 Primary endpoint events occurred in 155 patients (27.0%) in the selexipag group compared to 242 patients (41.6%) in the placebo group. Figure 2 illustrates the primary composite endpoint for both groups across the entire study period. The majority of events reported were disease progression and hospitalization, accounting for 81.9% in total. Subgroup analyses stratifying the selexipag group by doses revealed consistent treatment effects across doses.

With regard to secondary endpoints, overall, there were significantly fewer events with selexipag compared to placebo (HR 0.70, 95% CI 0.54 to 0.91).6MWD increases were observed in the selexipag group (median +4.0 m) while reductions were reported in the placebo group (median -9.0 m; treatment effect 12.0 m, 99% CI 1 to 24). There was no significant difference between groups in proportion of patients with worsening WHO functional class (odds ratio [OR] 1.16, 99% CI 0.81 to 1.66). At the end of the treatment period, death or hospitalization due to PAH were significantly reduced in the selexipag group (HR 0.70, 95% CI 0.54 to 0.91); 87.4% of these events were hospitalizations. However, there was no significant difference between groups in all-cause mortality (HR 0.97, 95% CI 0.74 to 1.28).
Figure 2. Primary composite endpoint in GRIPHON from baseline to study completion.10

Safety

In the GRIPHON study, 82 patients (14.3%) discontinued selexipag prematurely because of an adverse event, as compared to 41 patients (7.1%) receiving placebo (p<0.001).10 The most common adverse events leading to discontinuation were headache (65.2% vs. 32.8%), diarrhea (42.4% vs. 19.1%), and nausea (33.6% vs. 18.5%). Other adverse events leading to discontinuation were hyperthyroidism, hypotension, syncope, and major bleeding events. These events were more likely to occur during the 12-week dose titration phase, rather than during the maintenance phase. Additional adverse events reported more commonly with selexipag compared to placebo include jaw pain (25.7% vs. 6.2%), myalgias (16.0% vs. 5.9%), pain in the extremities (16.9% vs. 8.0%), flushing (12.2% vs. 5.0%), arthralgias (10.8% vs. 7.6%), and anemia (8.3% vs. 5.4%), all of which have been reported with prostacyclin therapies, in general.

Although not reported in GRIPHON, selexipag may cause pulmonary edema in patients with concomitant pulmonary veno-occlusive disease.3 If signs of pulmonary edema occur and are confirmed, discontinuation of selexipag is recommended. Though there are no adequate clinical trials demonstrating safety in pregnancy, animal data suggest selexipag does not cause adverse developmental effects to the fetus during organogenesis. Potential risks and benefits should be assessed by clinicians and discussed with patients prior to initiation of treatment in this population. Based on findings from animal studies, selexipag is not recommended in lactation; therefore, nursing mothers using selexipag are advised to either discontinue nursing or discontinue selexipag.

Dosing

Initiation of selexipag is recommended at 200 mcg twice daily, with or without food.3 The dose should be increased in increments of 200 mcg twice daily in weekly intervals, titrated up to a maximum of 1600 mcg twice daily or the maximally tolerated dose. No dose adjustment is required in patients with estimated glomerular filtration rate (eGFR) >15 mL/min/1.73 m²; no studies have been performed in patients undergoing dialysis or in patients with eGFR <15 mL/min/1.73 m². No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A); however, once daily dosing is recommended in patients with moderate hepatic impairment (Child-Pugh class B). Use of selexipag is not recommended in patients with severe hepatic impairment (Child-Pugh class C).
Conclusion

Given that PAH is severe and costly, special attention should be given to determine the appropriate therapeutic regimen for each patient. Although there are no head-to-head clinical trials comparing prostacyclin agonists, selexipag is the only oral treatment option shown to delay disease progression and reduce risk of hospitalization.3,11

References


Zurampic®: Filling the Gap in the Treatment of Hyperuricemia Associated with Gout

Amanda Pinski, PharmD

Introduction

Gout is considered 1 of the most common rheumatic diseases in the United States, affecting approximately 8.3 million people, and it is the most common cause of inflammatory arthritis in adults.1,2 Gout is a disorder that may result from hyperuricemia (defined as a serum urate level >6.8 or 7.0 mg/dL).1 Hyperuricemia can lead to the deposition of urate crystals in supersaturated extracellular fluids of the joints, causing the clinical and pathological features of the disease. Gout usually presents as episodic arthritis but can develop into chronic arthritis in 1 or more joints and result in the development of tophi. To improve signs and symptoms of gout, urate-lowering therapy (ULT) treatment guidelines suggest a target of a serum urate level of <6 mg/dL at minimum, with the common recommendation <5 mg/dL.

ULT is considered a staple in the management of gout.2 When ULT is effective, it is associated with a decreased risk of acute gouty attacks. Current guidelines for ULT in patients recommend a combination of non-pharmacologic therapy, such as diet and lifestyle modifications, in addition to pharmacologic therapy, based on patient-specific factors.1 First-line
pharmacological therapy includes allopurinol or febuxostat. Probencid is recommended as an alternative first-line agent if either allopurinol or febuxostat is contraindicated or not tolerated. If serum urate levels are not lowered to the recommended level, and the first-line agent is at the maximum appropriate dose, a uricosuric agent such as probencid, fenofibrate or losartan (off-label), may be added to therapy. If the patient still does not achieve recommended serum urate levels, pegloticase intravenous (IV) infusion may be added.

The inconvenience of probencid dosing, off-label use of medications, and IV infusion therapy are not ideal for patients requiring lower serum urate levels than can be achieved by a xanthine oxidase inhibitor alone. Zurampic® (lesinurad) has been approved by the Food and Drug Administration, in combination with a xanthine oxidase inhibitor, for treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid concentrations with a xanthine oxidase inhibitor alone.\(^3\)

Clinical Pharmacology

Lesinurad reduces serum uric acid levels by inhibiting the function of transporter proteins, uric acid transporter 1 (URAT1) and organic anion transportor 4 (OAT4) involved in uric acid reabsorption in the kidneys.\(^3,4\) URAT1 is responsible for most of the uric acid reabsorption from the renal tubular lumen and OAT4 is associated with the diuretic-induced hyperuricemia. Lesinurad has no action at the basolateral membrane of the proximal tubule cell. These actions lower serum uric acid levels and increase renal clearance and fractional excretion of uric acid.

In pharmacokinetic studies, 1 dose of lesinurad 200 mg daily in healthy subjects resulted in a mean maximum plasma concentration (C\(_{\text{max}}\)) and area-under-the-curve (AUC) of 6 µg/mL and 30 µg·hr/mL, respectively.\(^3,4\) Lesinurad has an absolute bioavailability of approximately 100% and is rapidly absorbed after oral administration. Lesinurad reaches C\(_{\text{max}}\) within 1-4 hours and administration with a high-fat meal decreases the C\(_{\text{max}}\) by 18%, with no alterations in AUC compared to the fasting state. In clinical trials, lesinurad was administered with food. Greater than 98% of the compound is bound to plasma proteins, mainly albumin, and this is not altered in patients with renal or hepatic impairment. Lesinurad has an elimination half-life of approximately 5 hours and does not accumulate after multiple doses. Lesinurad is metabolized in the liver by cytochrome P450 (CYP) 2C9. It is mainly excreted in the urine (63%) and feces (32%), and greater than 60% of the dose is excreted in the first 24 hours following administration. Approximately 30% of the dose is excreted in the urine unchanged.

Efficacy

The efficacy of lesinurad was studied in 3 trials: CLEAR 1, CLEAR 2, and CRYSTAL.\(^3,7\) The clinical studies included adults with hyperuricemia and gout; lesinurad was given in combination with the xanthine oxidase inhibitor, allopurinol or febuxostat. Patients received prophylaxis for gout flares with colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) during the first 5 months of treatment with lesinurad.

CLEAR1 and CLEAR2 were both 12-month, multicenter, randomized, double-blind, placebo-controlled, phase 3 studies in patients with gout who had elevated uric acid levels (≥6.5 mg/dL) despite a stable dose of allopurinol 300 mg/day (200 mg daily for those with moderate renal impairment) and at least 2 reported gout flares in the past 12 months.\(^3,5,7\) Patients were randomized 1:1:1 to receive allopurinol plus placebo, or allopurinol plus lesinurad 200 mg or 400 mg daily. The primary outcome was serum uric acid levels <6 mg/dL by month 6. Secondary outcomes included proportion of subjects treated for gout flares during months 6-12 and proportion of subjects with complete resolution of target tophus by month 12. Results, seen in Table 1, showed that allopurinol in combination with lesinurad 200 mg/day was superior to treatment with allopurinol alone. The reduction in serum uric acid levels to <6 mg/dL in the allopurinol plus lesinurad 200 mg group occurred at month 1 and was sustained throughout the 12-month period compared to serum uric acid levels in the placebo group.

CRYSTAL enrolled patients with gout and measurable tophi, treated with febuxostat 80 mg daily for 3 weeks.\(^3,4,6\) These patients were randomized in a 1:1:1 ratio to 1 of 3 groups: febuxostat 80 mg plus placebo, or febuxostat plus lesinurad 200 mg or 400 mg per day. Results, seen in Table 1, showed that lesinurad 200 mg in combination with febuxostat was not superior to placebo in reducing serum uric acid levels <5 mg/dL by month 6. However, average reduction in serum uric
acid levels in the febuxostat plus lesinurad 200 mg group was similar to that seen in the CLEAR 1 and 2 studies. Although these data are not shown, there was no statistically significant difference between the treatment and placebo groups in the proportion of patients who experienced a complete resolution of ≥1 target tophus.

In the 3 trials of lesinurad in combination with a xanthine oxidase inhibitor, there were no statistically significant differences between the treatment groups and placebo groups in the rates of gout flare between months 6 to 12. These results may be seen in Table 2.

Table 1. Primary endpoint results of the CLEAR 1, CLEAR 2, and CRYSTAL trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design &amp; duration</th>
<th>Enrollment</th>
<th>Treatment groups</th>
<th>Primary endpoint</th>
<th>Difference in proportion (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>CLEAR 1 (Study 301)</td>
<td>R, DB, MC, PC, P3 12 mos</td>
<td>N=603</td>
<td>ALLO + PBO</td>
<td>28%</td>
<td>LES200 vs. PBO 0.26 (0.17, 0.36)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ALLO + LES200</td>
<td>54%*</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ALLO + LES400</td>
<td>59%*</td>
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<tr>
<td>CLEAR 2 (Study 302)</td>
<td>R, DB, MC, PC, P3 12 mos</td>
<td>N=610</td>
<td>ALLO + PBO</td>
<td>23%</td>
<td>LES200 vs. PBO 0.32 (0.23, 0.41)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>ALLO + LES200</td>
<td>55%*</td>
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<td></td>
<td>ALLO + LES400</td>
<td>67%*</td>
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<tr>
<td>CRYSTAL (Study 304)</td>
<td>R, DB, MC, PC, P3, ITT 12 mos</td>
<td>N=324</td>
<td>FBX + PBO</td>
<td>47%</td>
<td>LES200 vs. PBO 0.10 (-0.03, 0.23)</td>
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<td>FBX + LES200</td>
<td>57%</td>
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<td></td>
<td>FBX + LES400</td>
<td>76%*</td>
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Table 2. Secondary endpoint results of the CLEAR 1, CLEAR 2, and CRYSTAL trials.

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<tr>
<th>Trial</th>
<th>Design &amp; duration</th>
<th>Enrollment</th>
<th>Treatment groups</th>
<th>Adjusted rate of gout flare requiring treatment per subject for months 6 to 12 (SE or SD)*</th>
<th>Incidence rate ratio (95% CI) vs. ALLO+PBO</th>
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</thead>
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<tr>
<td>CLEAR 1 (Study 301)</td>
<td>R, DB, MC, PC, P3 12 mos</td>
<td>N=603</td>
<td>ALLO + PBO</td>
<td>0.62 (0.11)</td>
<td>LES200 vs. PBO 0.99 (0.61, 1.61)</td>
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<td>ALLO + LES200</td>
<td>0.62 (0.11)</td>
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<td></td>
<td>ALLO + LES400</td>
<td>0.55 (0.11)</td>
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<tr>
<td>CLEAR 2 (Study 302)</td>
<td>R, DB, MC, PC, P3 12 mos</td>
<td>N=610</td>
<td>ALLO + PBO</td>
<td>0.89 (0.14)</td>
<td>LES200 vs. PBO 0.88 (0.57, 1.37)</td>
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<td>ALLO + LES200</td>
<td>0.78 (0.13)</td>
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<td>ALLO + LES400</td>
<td>0.83 (0.14)</td>
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<tr>
<td>CRYSTAL (Study 304)</td>
<td>R, DB, MC, PC, P3, ITT 12 mos</td>
<td>N=324</td>
<td>FBX + PBO</td>
<td>1.3 (0.25)</td>
<td>LES200 vs. PBO 1.2 (0.7, 2.1)</td>
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<td>FBX + LES200</td>
<td>1.5 (0.31)</td>
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<td>FBX + LES400</td>
<td>0.7 (0.15)</td>
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</table>

*Standard error represented for Clear 1 and Clear 2; standard deviation represented for CRYSTAL.
Safety

Contraindications, Warnings and Precautions

Lesinurad is contraindicated in patients with severe renal impairment (defined as estimated creatinine clearance [eCLcr] <30 mL/min), patients with end-stage renal disease, kidney transplant recipients, and patients on dialysis. Lesinurad is also contraindicated in patients with tumor lysis syndrome or Lesch-Nyhan syndrome.

Lesinurad should not be used as monotherapy for the treatment of hyperuricemia or prophylaxis of gout but should be used in combination with a xanthine oxidase inhibitor.

Renal events were associated with the use of lesinurad. A boxed warning is included in the drug label regarding acute renal failure with lesinurad use, with the focus on lesinurad monotherapy. Patients treated with lesinurad 200 mg daily in combination with a xanthine oxidase inhibitor had an increased incidence of serum creatinine elevations, most of which were reversible. Adverse reactions related to renal function occurred with initiation of lesinurad. A higher incidence of renal-related adverse reactions, including serious reactions of acute renal failure was observed with lesinurad 400 mg daily, the highest incidence occurring with monotherapy. Lesinurad should not be initiated in patients with eCLcr <45 mL/min. Renal function should be evaluated prior to initiation of therapy and periodically as indicated thereafter. More frequent monitoring for patients with eCLcr <60 mL/min or with serum creatinine elevations 1.5 or 2 times the pre-treatment value is recommended. If serum creatinine levels reach 2 times the pre-treatment values, lesinurad treatment should be interrupted. Patients receiving lesinurad who report symptoms indicative of acute uric acid nephropathy, such as flank pain, nausea, or vomiting, should interrupt treatment and serum creatinine should be measured promptly. Treatment should not be restarted without another explanation for the serum creatinine abnormalities.

In clinical trials, major cardiovascular events, defined as cardiovascular deaths, non-fatal myocardial infarctions, or fatal strokes, were observed with lesinurad. No causal relationship was established.

Adverse Events

Adverse events reported by the manufacturer are based on information derived from the CLEAR 1 and 2 and the CRYSTAL trials, investigating lesinurad 200 mg or 400 mg daily and placebo in a total of 511, 510, and 516 patients, respectively. The mean age of patients was 52 years, and the average duration of lesinurad therapy was 11.2 months. Sixty-three percent of the study population had mild-to-moderate renal impairment (eCLcr <90 mL/min).

The most common adverse events seen with lesinurad, reported in ≥2% of those treated with lesinurad in combination with a xanthine oxidase inhibitor and >1% of those in the placebo plus xanthine oxidase inhibitor group, were headache (5.3%), influenza (5.1%), and gastro-esophageal reflux disease (2.7%).

Lesinurad causes an increase in uric acid secretion, which can cause increases in serum creatinine, renal-related adverse reactions, and kidney stones. Among patients taking lesinurad 200 mg daily plus a xanthine oxidase inhibitor, 20 patients (3.9%) experienced an increase in serum creatinine 1.5 to <2 times greater than baseline, compared to 12 patients (2.3%) in the placebo group (p=not reported). By the end of the study, 18 patients (90%) in the treatment group had resolution of the elevated serum creatinine, compared to 9 patients (75%) in the placebo group. In patients taking lesinurad 200 mg daily plus a xanthine oxidase inhibitor, 9 patients (1.8%) experienced an increase in serum creatinine ≥2 times the baseline measurement, compared to 0 patients in the placebo group. By the end of the study, 8 patients (88.9%) in the treatment group had resolution of the elevated serum creatinine. Blood creatinine was increased in the treatment groups, with 22 patients (4.3%) in patients in the lesinurad 200 mg group, compared to 12 (2.3%) patients in the placebo group. Renal failure, including renal impairment, acute and chronic renal failure, and acute pre-renal failure, occurred in 11 placebo patients (2.1%), compared to 6 treatment group patients (1.2%), and nephrolithiasis occurred in 9 placebo patients (1.75) compared to 3 treatment group patients (0.6%).
In a 6-month, placebo-controlled, double-blind trial, patients on lesinurad alone experienced the following adverse events: renal failure (9.3%), blood creatinine increase (8.4%), nephrolithiasis (0.9%) and a ≥1.5 fold increase in serum creatinine.

**Drug-Drug Interactions**

Lesinurad exposure was increased when co-administered with CYP2C9 and in CYP2C9 poor metabolizers. Lesinurad should be used with caution in patients on moderate CYP2C9 inhibitors such as amiodarone and fluconazole. Lesinurad exposure was decreased when administered with moderate CYP2C9 inducers, such as rifampin and carbamazepine, resulting in a decreased therapeutic effect of lesinurad. CYP3A substrates such as sildenafil and amlodipine were reduced in healthy subjects when taken with lesinurad; atorvastatin was not affected, but sensitive HMG-CoA reductase inhibitors may be affected. The efficacy of CYP3A substrates may be affected by lesinurad and should be monitored. *In vitro* studies suggest that lesinurad does not inhibit epoxide hydrolase, but inhibitors of epoxide hydrolase, such as valproic acid, may interfere with metabolism of lesinurad. Hormonal contraceptives may not be effective when taking lesinurad, therefore women should practice additional methods of contraceptive in addition while taking lesinurad. Aspirin at high doses (>325 mg/day) may decrease the efficacy of lesinurad in combination with allopurinol.

**Dosage and Administration**

Lesinurad should be administered orally with a xanthine oxidase inhibitor, such as allopurinol or febuxostat. The recommended dosing of lesinurad is 200 mg daily in the morning with food and water, and the maximum daily dose is 1 tablet (200 mg). Lesinurad is not recommended in patients taking less than 300 mg of allopurinol daily, or 200 mg if the eCLcr is <60 mL/min. If treatment with the xanthine oxidase inhibitor is interrupted, treatment with lesinurad should be interrupted, as well. Failure to do so could result in an increased risk for renal events. Patients taking lesinurad should be instructed to stay well-hydrated with 2 L or 68 oz of liquid per day.

Dose adjustments are not required for patients with mild-to-moderate renal dysfunction (eCLcr <45 mL/min). Patients should have renal function monitored prior to the start of lesinurad therapy and as clinically indicated thereafter. Patients with eCLcr <60 mL/min should be monitored more frequently and therapy should be discontinued in patients with consistent eCLcr <45 mL/min.

Gout flares may occur after initiation of therapy with lesinurad. Gout flare prophylaxis is recommended in patients initiating therapy. Gout flares do not necessitate the discontinuation of the medication and should be managed as deemed clinically appropriate for each patient.

**Summary**

Lesinurad is a new option for patients on a xanthine oxidase inhibitor alone with uncontrolled serum uric acid levels. While lesinurad offers convenient dosing, the adverse effects on renal function may deter some patients from therapy. Still, lesinurad is viable as an alternative to lifestyle modification for patients suffering from gout with hyperuricemia uncontrolled on a xanthine oxidase inhibitor alone.

**References**


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Adult Immunizations: What’s New?

Esra Mustafa, PharmD

In October 2015, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) approved the 2016 immunization schedule for adults in the United States (US) aged ≥19 years.¹ There are several new recommendations in the 2016 schedule including the addition of recently licensed meningococcal serogroup B (MenB) and human papillomavirus (HPV) vaccines and a revision to the dosing interval for the pneumococcal vaccination. These recommendations are described below.

**Pneumococcal Vaccination: Extending the Dosing Interval**

The Food and Drug Administration (FDA) has approved 2 pneumococcal vaccines for adults: the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23).² In August 2014, the ACIP recommended that a dose of PCV13 be followed by a dose of PPSV23 in all adults aged ≥65 years who have not previously received the vaccine. In 2015, they asserted that the recommended interval between the 2 vaccinations differs depending on the patient’s risk factors and the order in which the 2 vaccines are given.³ The ACIP changed the recommended interval for the PCV13-PPSV23 sequence from 6-12 months to ≥1 year for immunocompetent adults aged ≥65 years (see Figure 1).

No other changes were made to the recommended intervals for all other age and risk groups.³ An interval of ≥8 weeks is recommended for adults of all ages with immunocompromising conditions, cerebrospinal fluid leaks, or cochlear implants.

The ACIP recommends that the 2 pneumococcal vaccines should not be co-administered.³ However, if a dose of PPSV23 is given earlier than the recommended interval, the dose does not have to be repeated. For patients in whom PPSV23 is administered first, the ACIP recommends waiting ≥1 year and then administering PCV13.
Figure 1. Current ACIP recommendations on intervals for sequential use of PCV13 and PPSV23 in immunocompetent adults aged ≥65 years.³

PCV13=13-valent pneumococcal conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine

**What is the Rationale for the Change in Interval?**

The ACIP reviewed immunogenicity studies to determine whether the recommended interval for the PCV13–PPSV23 sequence for immunocompetent adults aged ≥65 years should be changed, to simplify the recommendations and allow for easier implementation of the vaccine schedule in clinical practice.³

The ACIP evaluated 8 studies comparing immune responses in immunocompetent adults aged ≥50 years after a PCV–PPSV23 sequence with responses for those who received PCV or PPSV23 alone.⁴⁻¹¹ Four studies demonstrated greater or equivalent antibody responses following PCV7–PPSV23 doses given 6 months apart compared to responses following PCV7 or PPSV23 alone.⁵,⁶,⁹,¹⁰ In another study, patients who received the polysaccharide vaccine 1 year after the conjugate vaccine had improved responses when compared to those who received a single PPSV23 dose.¹¹ Two studies found that patients who had a 3-4 year interval between the vaccines had increased immune responses to a larger number of serotypes when compared to those that had a 1-year interval between vaccines.⁴,⁷ In a separate study, 2-month and 6-month intervals between PCV7 and PPSV23 administration were compared;⁸ there were no significant differences between groups in immune responses, but there was a higher incidence of injection site swelling in the group with the 2-month interval between doses.

Based on their evaluation, the ACIP stated that shorter intervals (e.g., 8 weeks) between vaccines may be associated with greater injection site reactions compared with longer intervals, and sequential administration with longer intervals (≥1 year) may improve immune responses, compared to responses following single doses.⁹ Extension of the interval for the PCV13-PPSV23 sequence to ≥1 year in immunocompetent adults aged ≥65 years simplifies the ACIP recommendations for pneumococcal vaccine administration in that the dosing interval between pneumococcal vaccines is the same regardless of the order in which the 2 vaccines are given. This may allow for greater adherence to the immunization schedule as many patients follow up with their providers on a yearly basis.
New Meningococcal B Recommendations

There are 5 main serogroups of meningococcal disease: A, B, C, W, and Y. Per the CDC, serogroups B, C, and Y are the major causes of meningococcal disease in the US. Until recently, available meningococcal vaccines (polysaccharide (MPSV4) or conjugate [MenACWY]) only covered serogroups A, C, W, and Y. In 2013, there were outbreaks of MenB disease on 2 college campuses, leading to expedited development and FDA review of MenB vaccines. The FDA approved 2 MenB vaccines, MenB-FHbp (Trumenba®) and MenB-4C (Bexsero®), in 2014 and 2015, respectively. Approval of the MenB-FHbp vaccine was based on the demonstration of immune response, as measured by serum bactericidal activity against 4 of the most prevalent serogroup B strains in the US. Approval of the MenB-4C was based on the demonstration of immune response against 3 serogroup B strains. Both vaccines were found to be safe, with the most common side effects being pain at the injection site, headache, myalgia, fatigue, induration, nausea, chills, and arthralgia. Both vaccines were approved for use in individuals aged 10 through 25 years. Suggested dosing is described in Table 1.

In February 2015, the ACIP expanded use of MenB vaccines to persons aged ≥10 years who are at increased risk for MenB disease. Patients at increased risk include those with complement deficiencies, anatomic or functional asplenia, and those exposed to an outbreak. Microbiologists who work routinely with Neisseria meningitidis isolates are also at increased risk for meningococcal disease.

Table 1. Approved MenB vaccines.

<table>
<thead>
<tr>
<th>Vaccine*</th>
<th>Brand name</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>MenB-FHbp</td>
<td>Trumenba®</td>
<td>0.5 mL</td>
<td>Intramuscular</td>
<td>3 doses at 0, 2, and 6 months</td>
</tr>
<tr>
<td>MenB-4C</td>
<td>Bexsero®</td>
<td></td>
<td></td>
<td>2 doses, 1 month apart</td>
</tr>
</tbody>
</table>

*The 2 vaccines are not interchangeable; the same vaccine product must be used for all doses.

Each year in the US, approximately 50 to 60 cases of MenB disease are reported among adolescents and young adults aged 11 to 23 years. Over 80% of these cases occur in older adolescents and young adults aged 16 to 23 years. While outbreaks have been reported on college campuses, MenB infections are not limited to college students; 30%-60% of cases occur in young people who are not in college.

The ACIP evaluated immunogenicity and safety data from 7 clinical trials for MenB-FHbp and 5 clinical trials for MenB-4C. Vaccine efficacy was determined based on serum bactericidal activity with human complement (hSBA); immunogenicity was defined as the proportion of subjects achieving ≥4-fold increase in hSBA for each serogroup B strain and the proportion of subjects achieving titers exceeding the lower limit of quantification for each strain. In the studies of MenB-FHbp and MenB-4C, the majority of study participants demonstrated a composite response. Among the participants receiving MenB-FHbp, 1 month following the third dose, 81.0%-83.9% had a composite response to all 4 tested strains. Among the participants receiving MenB-4C, 1 month following the second dose, 90-94% had a composite response to the 3 tested strains. Few serious vaccine-related adverse events were reported and all resolved with no sequelae.

The ACIP recommends administration of the MenB vaccine to adolescents and young adults aged 16 to 23 years to provide short-term protection against most strains of MenB disease. They estimate that 15 to 29 cases and 2 to 5 deaths could be prevented annually with routine MenB vaccination at ages 11, 16, or 18 years. In comparison, limiting routine vaccination to college students-only is estimated to prevent 9 cases and 1 death per year. The preferred age for MenB vaccination is 16 to 18 years; administration at this age range may increase the likelihood of MenB disease prevention in the highest age-related risk period. Currently, there is not enough evidence to make a routine recommendation that all adolescents be vaccinated with the MenB vaccine; individual clinical decision-making is encouraged.

The MenB vaccines may be administered concomitantly with other vaccines but at different anatomic sites. Notably, the safety and effectiveness of the MenB vaccines have not been established in pregnant or lactating women; vaccination in this population should be deferred unless patients are deemed at increased risk of meningococcal disease. Post-
marketing studies are necessary to further determine the safety and effectiveness of the vaccines and will be reviewed by the ACIP as they become available.

Addition of 9-Valent HPV (9vHPV) Vaccine

HPV is the most common sexually-transmitted infection.\(^{16}\) Though most infected patients are asymptomatic, the virus has been associated with cervical, vulvar, and vaginal cancer in females, penile cancer in males, and anal cancer and oropharyngeal cancer in both females and males. Additional risks of HPV infection include cervical precancers, including cervical intraepithelial neoplasia (CIN) grade 2 or 3 and adenocarcinoma in situ. There are >150 types of HPV, of which approximately 40 involve the genitalia. Genital HPV types are classified as high-risk or low-risk according to their association with cancer. Approximately 64% of the invasive HPV-associated cancers are attributable to HPV types 16 and 18.\(^{17}\) HPV types 6 and 11 cause >90% of anogenital warts. About 10% of invasive HPV-associated cancers are attributable to HPV types 31, 33, 45, 52, and 58. Approximately 50% of CIN2+ cases are caused by HPV types 16 or 18 and 25% by HPV types 31, 33, 45, 52, or 58.

Currently available HPV vaccines are listed in Table 2. All 3 vaccines contain virus-like particles (VLPs) of strains 16 and 18.\(^{17}\) Gardasil® also covers against types 6 and 11 which are responsible for most anogenital warts. In December 2014 the 9vHPV (Gardasil® 9) vaccine was approved by the FDA. This vaccine contains VLPs for 5 additional HPV strains that are responsible for 10% of invasive cancers.

Table 2. Available HPV vaccines.\(^{17}\)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Brand name</th>
<th>Covered strains (VLP contents)</th>
<th>Dose</th>
<th>Route</th>
<th>Dosing schedule*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalent (2vHPV)</td>
<td>Cervarix®</td>
<td>16, 18</td>
<td>0.5 mL</td>
<td>Intramuscular</td>
<td>3 dose series at 0, 1, 6 months</td>
</tr>
<tr>
<td>Quadrivalent (4vHPV)</td>
<td>Gardasil®</td>
<td>6, 11, 16, 18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-valent (9vHPV)</td>
<td>Gardasil® 9</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, 58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VLP=virus-like particle

*If interrupted, the series does not need to be restarted.

The ACIP evaluated the efficacy, immunogenicity, and safety of 9vHPV.\(^{17}\) The vaccine was compared to 4vHPV in a phase 3 trial for prevention of CIN2 or 3, and vulvar or vaginal intraepithelial neoplasia grades 2 or 3 caused by HPV. The efficacy of the 9vHPV vaccine was found to be 96.7% for the prevention of CIN2, vulvar intraepithelial neoplasia grade 2 or 3, and vaginal intraepithelial neoplasia grade 2 or 3 caused by HPV 31, 33, 45, 52, or 58. Immunogenicity of 9vHPV was found to be non-inferior to that of 4vHPV based on a comparison of antibody titers measured 1 month after the third dose.

The 9vHPV vaccine was well tolerated in clinical trials; the most common side effects were injection site-related pain, swelling, and erythema that were mild to moderate in intensity.\(^{17}\) In clinical trials it appeared that the 9-valent vaccine caused slightly more injection site reactions than the quadrivalent vaccine. Notably, both the 9-valent and quadrivalent vaccines are manufactured using Saccharomyces cerevisiae (yeast); therefore, these vaccines should not be administered to patients with a hypersensitivity to yeast.

Adolescents should be routinely vaccinated against HPV at age 11 or 12, however the vaccine series may be started as early as age 9 years.\(^{16}\) Females aged 13 through 26 years and males aged 13 through 21 years not vaccinated previously should also receive the HPV vaccine. Vaccination is also recommended through age 26 years for men who have sex with men and for immunocompromised persons if they have not been previously vaccinated or if they have not completed the series. The ACIP has given no preference to 1 HPV vaccine over the others in female patients. Females may be vaccinated with the bivalent, quadrivalent, or 9-valent vaccine. Males should be vaccinated with the quadrivalent or the 9-valent vaccine.

The HPV vaccines should be administered in a series of 3 doses.\(^{17}\) If, when completing the series, the vaccine product previously administered is not known or not available, any available HPV vaccine may be used to continue or complete
the series for females for protection against HPV types 16 and 18. However, the ACIP advises using the 9-valent or quadrivalent vaccine to continue or complete the series in males. If the vaccine schedule is interrupted, the vaccination series does not need to be restarted. It is reasonable to recommend the 9vHPV vaccine to start and complete a series as it provides coverage against additional high-risk HPV strains compared to the other HPV vaccines.

Summary

The 2016 ACIP-recommended adult immunization schedule incorporates a few notable changes from the 2015 schedule, including an increase in dosing interval for pneumococcal vaccination, addition and expansion of MenB vaccine use, and addition of the 9vHPV vaccine. The extension of the dosing interval between pneumococcal vaccines for most healthy adults allows for easier implementation of the vaccine schedule in clinical practice. Administration of the MenB vaccine will ensure adolescents and adults receive protection against most strains of MenB disease. Finally, inclusion of the 9vHPV vaccine in the new schedule is important in that the 9vHPV vaccine protects against additional HPV types compared to the quadrivalent and bivalent HPV vaccines.

References


New Boxed Warning on Essure®: A Review of Clinical Data
Samantha Will, PharmD

Introduction

Essure® is a medical device approved by the Food and Drug Administration (FDA) in 2002 as a permanent birth control solution for women seeking to undergo non-surgical sterilization.1 Essure® is a spring-shaped coil composed of nickel-titanium alloy which is inserted bilaterally into a woman’s fallopian tubes using a hysteroscope.2 Over a period of 3 months, tissue growth occurs around the inserts, preventing ovum fertiliation through occlusion of the fallopian tube (see Figure 1). To date, Bayer has reported that about 750,000 women are using Essure®; last year, the FDA found >5,000 reports of adverse events associated with the device, prompting further review of its benefits and risks.3

Figure 1. Placement of Essure®.2
Boxed Warning

In September 2015, the FDA convened an Advisory Committee meeting to hear expert scientific and clinical opinions as well as patient experiences regarding Essure® and issued a public docket to solicit comments on the device. After careful review of this feedback and additional medical literature published or received since the meeting, the FDA published draft guidance requiring the addition of a boxed warning to Essure® labeling as well as a patient safety checklist to be discussed by the patient and provider. The draft guidance is available for review and comment for 60 days from its initial publication; the guidance will subsequently be updated and applied to the device as the FDA deems fit. The draft language for the boxed warning may be seen in Figure 2.

Figure 2. Draft boxed warning on Essure®.

The patient checklist has been drafted to include various counseling points, clinical information, as well as documented adverse reactions, and is intended to fully inform the patient about the risks and benefits of the device. Additionally, the checklist stresses permanence of the device and its effects and the importance of adherence to the post-Essure® hysterosalpingography (HSG) procedure to establish tubal occlusion. Characteristics of Essure® placement and alternative sterilization procedures (e.g., tubal ligation) are listed, including complications from Essure® potentially leading to the need for a second procedure or removal through an abdominal incision.

The FDA states that the patient decision checklist should be reviewed and signed by the patient and healthcare provider; the original document should be retained in the patient records at the provider’s office, and a copy should be given to the patient. The FDA also mandated that the manufacturer of the device conduct a post-marketing study evaluating the benefits and risks of Essure®.

Safety Concerns

Per the FDA’s Manufacturer and User Facility Device Experience (MAUDE) database, from November 2002 through December 2015, there were 9,900 issues reported related to Essure®. The most commonly reported adverse reactions were pain or abdominal pain (n=6,989), heavier menses/menstrual irregularities (n= 3,210), headache (n = 2,990), fatigue (n= 2,159), and weight fluctuations (n=2,088). Most reports listed multiple problems per patient. Device-related problems were also reported, including patient-device incompatibility (e.g., possible nickel allergy; n=2,016), device migration (n=854), and device breakage (n=429). Additional cases of device failure were reported: there were 631 reports of pregnancy in patients using Essure®, of which 150 resulted in live births and 294 resulted in pregnancy losses. Among the 294 pregnancy losses, there were 96 ectopic pregnancies.

In addition to these reports, findings from a population-based cohort study published in the British Medical Journal in September 2015 contributed to the FDA’s decision to add a boxed warning to the Essure® label. Mao et al sought to determine the safety and efficacy of hysteroscopic sterilization versus laparoscopic tubal ligation, the traditional procedure employed for female sterilization prior to approval of Essure®. The investigators identified women in New York State receiving either procedure between 2005 and 2013 using data from the New York State Department of Health Statewide Planning and Research Cooperative System. Outcomes included procedure time and total charges, unintended pregnancy, ectopic pregnancy, and reoperation. Follow-up for most analyses was limited to 1 year; unintended pregnancy and reoperation was evaluated within 2-3 years.
During the study period, 8,048 women underwent hysteroscopic sterilization and 44,278 women underwent laparoscopic sterilization. An increase in the frequency of hysteroscopic sterilization was observed during this period, from 45 cases to 1,231 cases (0.6% to 25.9% of all procedures, p<0.01; see Figure 3). The majority of women undergoing sterilization were aged 30-39 years (55.2%) and were members of a commercial insurance plan (55.9%). Comparing groups by procedure, a greater proportion of women undergoing hysteroscopic sterilization were aged ≥40 years (25.2% vs. 20.5%, p<0.01) and were enrolled in Medicaid (43.6% vs. 37.1%, p<0.01). Compared to patients undergoing laparoscopic sterilization, women undergoing hysteroscopic sterilization also had a higher prevalence of previous pelvic inflammatory disease (10.3% vs. 7.2%, p<0.01) and history of major abdominal surgery (9.4% vs. 7.9%, p<0.01).

Hysteroscopic procedures were of shorter duration compared to laparoscopic procedures (median duration 36 min vs. 52 min, p<0.01) but higher charges (median $7,832 vs. $5,068, p<0.01). Surgical complications and major medical complications of both procedures were rare (<0.5%). Unintended pregnancy rates were similar in both the hysteroscopic and laparoscopic arms (1.2% vs 1.1%, respectively, p=0.66); however, the need for reoperation within the first year after the procedure was significantly higher in the hysteroscopic sterilization population (2.4% vs 0.2%, p<0.01), representing a 10-fold increased risk or an additional 21 operations per 1000 patients. The odds of reoperation at 2 and 3 years post-hysteroscopic sterilization were also higher (odds ratio [OR] 7.96, 95% confidence interval [CI] 6.00 to 10.57, and OR 5.88, 95% CI 4.44 to 7.79, respectively). While the reoperation procedures could have been performed due to unplanned pregnancy, women undergoing laparoscopic and hysteroscopic procedures had similar pregnancy outcomes within the study. Thus, it can be inferred that reoperation was conducted to address device complications, such as migration and hypersensitivity reactions, reflected in the MAUDE database.

Figure 3. Number of hysteroscopic sterilization and laparoscopic sterilization procedures conducted between 2005 and 2013 in New York State.

Adherence

An increased risk for device-related adverse events and unintended pregnancy may be attributed to lack of follow-up after Essure® placement. After the device has been placed, HSG is recommended to ensure proper placement and confirm tubal occlusion. Until this test, referred to as the Essure® Confirmation Test, is conducted, patients are advised to continue using alternative contraception. While patient adherence to post-Essure® placement HSG is not well-established, studies have been conducted to characterize adherence to the procedure in low-income populations. Howard et al conducted a retrospective chart review of patients who underwent Essure® placement at the Truman Medical Center in Kansas City, Missouri. They sought to identify predictive factors for adherence to post-Essure® HSG. Predictor variables assessed included age, parity, and method of alternative contraception. A total of 132 patients were referred for HSG. Most patients included in the study were publically insured (89.0%) and unmarried (76.7%). Only 70 patients (53%) presented for follow-up HSG. Multivariate analyses revealed that age and parity were independently associated with HSG adherence. Women aged ≥35 years had higher odds of adherence to HSG compared to women aged <35 years (OR=3.72, 95% CI 1.35 to 10.23); women with ≥3 children had lower odds of adherence compared to those with <3 children (OR=0.36, 95% CI 0.16 to 0.82). Women aged <35 years with ≥3 children had the lowest adherence rate (36.4%); no association was found between parity and adherence in women aged ≥35 years.
In another retrospective chart review, Shavell et al evaluated adherence to post-Essure® HSG in patients who underwent Essure® placement at a University teaching hospital in Detroit, Michigan. Patients in this study were counseled on the need for post-Essure® HSG at multiple time points, including prior to the scheduling of Essure® placement, the day of Essure® placement, and at the postoperative visit. Various factors including age, gravidity, and parity were compared between patients who were adherent to HSG and those who were non-adherent. Placement of Essure® was successfully completed in 79 patients. Among them, only 10 patients (12.7%) underwent HSG. No significant differences were observed between adherent patients and non-adherent patients in all factors assessed, including age, race, body mass index, gravidity, parity, history of pelvic inflammatory disease, tobacco use, illicit drug use, type of insurance, or distance from the hospital. One case of unintended pregnancy was documented in a patient who was non-adherent to post-Essure® HSG.

Importantly, verification of bilateral tubal occlusion through HSG is part of the FDA-approved process for confirming device safety and efficacy; non-adherence to HSG may increase the risk for unintended pregnancy and otherwise detectable and preventable adverse reactions such as ectopic pregnancies and perforated coils.

Conclusion

While controversy has arisen surrounding the use of Essure®, the device remains a viable method of permanent sterilization and is a non-invasive alternative to tubal ligation. The FDA has updated labeling requirements to incorporate an educational tool and boxed warning highlighting the risks and benefits of the device observed in post-marketing studies. The FDA has mandated Bayer to conduct further post-marketing studies evaluating the safety and efficacy of the device. When considering placement of Essure®, physicians should continue to screen patients for appropriateness and continue to stress the importance of adhering with follow-up visits to ensure safety and effectiveness.

References

Providing Clarity: Evidence for the Efficacy and Safety of New York State’s New Medical Marijuana Law, with a Focus on Neuropathic Pain

Benjamin S Kematick, PharmD

Introduction

On January 6, 2016, the medical marijuana law went into effect in New York State (NYS), providing limited access to patients with specific severe, debilitating or life-threatening conditions accompanied by an associated or complicating condition (see Table 1). Under the NYS Compassionate Care Act, these patients may now have an additional therapeutic option for the management of these conditions.

Table 1. Selected indications for medical marijuana in NYS.

<table>
<thead>
<tr>
<th>Conditions approved in NYS</th>
<th>Conditions under review for inclusion in NYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Muscular dystrophy</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (Lou Gehrig’s disease)</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>PTSD</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Spinal cord damage causing spasticity</td>
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<tr>
<td>Epilepsy</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td>Huntington’s disease</td>
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</tr>
</tbody>
</table>

AIDS=acquired immunodeficiency syndrome; HIV=human immunodeficiency virus; NYS=New York State; PTSD=post-traumatic stress disorder

Certified patients with these conditions can obtain a prescription from a certified physician for medical marijuana in the forms of capsules, liquids, or oils for use orally or via vaporization. Smoking is prohibited. This legislation has been praised for being a “significant step forward” but has been criticized for being overly restrictive. NYS joins 24 other states and the District of Colombia with laws regulating the dispensing of medical marijuana. Medical marijuana is a hot topic in both public policy as well as in healthcare, and there are many different opinions of its current place in medicine. With access to medical marijuana expanding in NYS it is important for pharmacists to understand the therapeutic benefits and risks that medical marijuana can represent to our patient population. Being up-to-date with the available safety and efficacy data will allow pharmacists to provide evidence-based care for their patients. This article is aimed at providing pharmacists with up-to-date information regarding the approved uses of marijuana for management of selected diseases/conditions, in particular, neuropathic pain.

Efficacy

For the approved indications there are a small number of studies suggesting the efficacy of medical marijuana as an adjunct therapy to standard care. However, the degree to which marijuana is efficacious is highly variable; there are only small studies of patients involving different formulations of marijuana dispensed to patients over short periods of time. A few systematic reviews and meta-analyses have been conducted to further evaluate its efficacy and safety.

The endocannabinoid system has been implicated in the sensation of neuropathic pain, both central and peripheral. Actions on the cannabinoid (CB)-1 and CB-2 receptors may affect the perception of neuropathic pain. In 2015, Andreae et al performed a meta-analysis evaluating efficacy of inhaled cannabis for chronic neuropathic pain and found that in the short term, inhaled cannabis can improve pain in up to 1 out of 5-6 patients. The study included 5 randomized controlled trials and 178 patients. Studies were included if they were randomized and controlled; however, due to the nature of the intervention, blinding was not considered necessary. The analysis grouped patients into responders and non-responders to attempt to quantify a clinically significant effect. Response to therapy was defined as >30% reduction in neuropathic pain. Outcomes were observed in the 5 studies over periods ranging from 5 hours up to 2 weeks; the observed effect across the
5 studies was comparable to that of gabapentin and other available options for neuropathic pain. Notably, the studies included in this meta-analysis were short in duration. Long-term, randomized controlled trial data are not available at this point.

Two of the studies included in Andrae et al’s meta-analysis involved patients with human immunodeficiency virus associated sensory neuropathy (HIV-SN). HIV-SN is difficult to treat, as it is refractory to many conventional neuropathic pain therapies. However, in a different meta-analysis evaluating the efficacy of various treatments in HIV-SN, Phillips et al found that smoked cannabis was shown to be one of the only effective therapies. Similar to the previously referenced meta-analysis, patients in this study were designated as responders or non-responders, with response defined as ≥30% reduction in pain. Outcomes were observed in both studies (n=122 patients, 61 treated with cannabis) over a period of 5 days. This analysis demonstrated a marked improvement in pain over placebo, with a pooled number-needed-to-treat of 3.38. However, in both of the trials, there was a high chance of unblinding in the treatment groups due to previous patient experience with marijuana. The meta-analysis was not able to report superiority over placebo in HIV-SN for commonly used neuropathic pain treatments like gabapentin, pregabalin, amitriptyline, or lamotrigine.

Notably, the studies evaluated by Phillips et al showed potential efficacy of marijuana use when smoked. Currently, the compassionate care law in NYS only pertains to other forms of marijuana consumption, including capsules, liquids and oils. In a systematic review, Lynch et al. found that a preparation intended to be given as a buccal spray containing equal ratios of cannabidiol (CBD) to tetrahydrocannabinol (THC) administration provided analgesic effect in 6 of 7 trials. This preparation is commercially available as Sativex® in Canada and is indicated for neuropathic pain and spasticity in multiple sclerosis and moderate-to-severe cancer pain. This is important, as 1 of the preparations that NYS is requiring all dispensaries to carry must contain an equal ratio of CBD to THC. It is hard to draw conclusions on 1 preparation compared to another, especially when dispensaries may prepare products in different manners, but there are some data to suggest that non-smoked forms of marijuana can potentially be efficacious in the treatment of pain. It has been noted that oral preparations of marijuana and marijuana analogs show reduced bioavailability of THC as compared to smoked marijuana, ranging from 5-20%, and a maximum plasma concentration of only 20% of smoked marijuana. As such, when patients are taking enteral preparations of marijuana sold in NYS, there may be an expected difference in efficacy when compared to findings from studies primarily focused on inhaled or buccally administered marijuana.

Safety

A number of safety concerns exist with the use of marijuana, including increased risk of psychiatric issues, respiratory effects, cognitive impairment, and cardiovascular toxicities. In a review of the literature, Kalant found that the most frequently reported side effects with medical marijuana consumption were dizziness or lightheadedness (30-60%), dry mouth (10-25%), fatigue (5-40%), muscle weakness (10-25%), myalgia (25%) and palpitations (20%). Importantly, any medication associated with cognitive effects can also impair the ability to drive and operate machinery. Marijuana is increasingly suspected among those driving under the influence of drugs other than alcohol, with studies in Europe estimating a rate as high as 57%. THC rapidly passes from the blood into the brain and other tissues, so there is not a close relationship between blood levels of THC and impairment, as with alcohol. Experimental studies have shown that marijuana exposure produces moderate but clear impairment of driving skills. While this impairment does not seem to be as strong as that seen with alcohol, patients on marijuana need to be counseled not to operate motor vehicles or heavy machinery while using the medication. This is the same as if they were taking opiates or other medications that have the potential to impair cognitive function.

Marijuana use in patients can also exacerbate psychiatric events, in particular, schizophrenia. In patients with schizophrenia, marijuana use has been associated with a higher percentage of active symptoms like hallucinations as well as more intensive courses of treatment. In a retrospective cohort study of over 50,000 Swedish soldiers, those using cannabis were 20% more likely to develop schizophrenia compared to those not using cannabis over their lifetimes; frequent (>50 times) cannabis users were over 600% more likely to develop schizophrenia. The frequency of schizophrenia overall (0.71%) was relatively small; however, it was significantly associated with cannabis use (p<0.001). As such, caution is advised when considering marijuana use in patients with a history of schizophrenia. Additionally, in a review of the literature, Degenhardt et al concluded that heavy cannabis use at an early age (childhood adolescence and
Acutely, marijuana use can cause an increase in heart rate, increase in blood pressure, and increased workload requirements for cardiac muscle.\textsuperscript{13} There have been case reports of cannabis use in patients with pre-existing cardiovascular risk experiencing acute myocardial infarction, as well as those with advanced disease experiencing transient ischemic attack.\textsuperscript{16} Similarly, there is the potential for exacerbation of arrhythmias in patients concurrently taking other drugs which can affect heart rhythm and rate. In adolescent patients receiving tricyclic antidepressants, moderate-to-severe tachycardia, confusion, and delirium were noted.\textsuperscript{17} Thus, caution is advised when administering medical cannabis in patients at higher risk of cardiovascular disease or those on medications which can exacerbate these conditions. Acute respiratory effects have also been noted with long-term smoking of marijuana, including increased inflammatory changes in the lungs. In NYS, the preparations of marijuana to be consumed by patients should not be smoked; vaporization of marijuana is less certain to cause those changes but still must be considered.\textsuperscript{13} Administration of vaporized preparations in patients with underlying pulmonary disease may not be appropriate for this reason. As far as potential pharmacokinetic interactions are concerned, marijuana itself does not seem to have clinically significant drug interactions in the cytochrome P450 (CYP) system. Administration via smoking will induce CYP1A2; however, this is less of a concern in this region since this route of administration is prohibited in NYS. Most relevant interactions with marijuana use will likely be related to pharmacodynamics of marijuana and other medications, particularly in additive cognitive impairment and possibly with increased cardiotoxicity.\textsuperscript{12}

\textbf{Current Practice}

In NYS, the practice of providing medical marijuana to eligible patients is new and unfamiliar to many practitioners. Most of the evidence supporting the efficacy of marijuana is for the route of smoking, which is prohibited by the new law. Additionally, most of the data on marijuana for the relief of neuropathy were observed on a short time scale, ranging from hours to weeks. Long-term data on efficacy of marijuana for pain relief are currently not available. NYS-approved preparations of medical marijuana will have fundamentally different characteristics in absorption and maximum concentrations compared to those seen with smoking. The existing data will therefore not necessarily be directly applicable to the formulations available in NYS.

While most adverse events are considered mild, there is concern for long-term use of marijuana. Also, it should be noted that many of these adverse events have been reported among individuals smoking the plant for its psychoactive effects, at much higher doses than those typically needed for analgesia. Concern could possibly be mitigated.\textsuperscript{4} As it stands now, any prescription for marijuana must be dispensed at 1 of 20 dispensaries throughout NYS, and all dispensings must be accompanied by prescriptions and uploaded to the Prescription Monitoring Program (PMP) within 24 hours, similar to other controlled substances in NYS.\textsuperscript{1} While most community pharmacists will not be involved in the direct dispensing of the medical marijuana, they should have access to the records of each dispensing, through the PMP.

If a pharmacist were to see a medical marijuana dispensing on the PMP, possible drug interactions leading to additive central nervous system depression and, possibly, additive cardiotoxicity and pulmonary toxicity if vaporized must be considered. Diligent monitoring of patient-reported changes and appropriate use of medical marijuana, at the lowest effective dose for the shortest amount of time, may provide benefit that is missing from current available therapy, particularly in refractory neuropathic pain like HIV-SN. If the included indications expand, then relevant data will need to be reviewed as well. For now, the effects of NYS’ new medical marijuana law will require evaluation. Unfortunately, not all of the preparations that were used in the available studies are approved for use in NYS. However, expanded access to a potentially beneficial drug is interesting, and medical marijuana may be an additional option for therapy in patients who might desperately need it.
References


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