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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.

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**Breathe Easy with Afrezza®?**
Alyssa Pignato, PharmD

Afrezza® (Technosphere® insulin) inhalation powder was recently approved by the Food and Drug Administration (FDA) for the treatment of type 1 and 2 diabetes mellitus. Afrezza® is not the first inhaled insulin product to be marketed in the United States (US); the drug is preceded by Pfizer’s Exubera®, which was voluntarily withdrawn due to market failure in 2007.

There are several differences between Exubera® and Afrezza®, the most notable being the inhalation device. Unlike the cumbersome Exubera® inhaler, Afrezza® utilizes the Gen2 inhaler, a whistle-sized device in which the patient loads a single-use cartridge containing Technosphere® insulin.\(^1\) Dosing is also more convenient. Exubera’s® milligram strength posed a challenge for dose conversion and titration, whereas Afrezza® cartridges are formulated in insulin units, allowing for convenient dose transition from injectable mealtime insulin.\(^1,2\)
Clinical pharmacology

Afrezza® consists of human insulin (isolated from non-pathogenic Escherichia coli) microencapsulated within a carrier excipient known as fumaryl diketopiperazine (FDKP) and an inhaler device (Gen2).2-4 The mildly acidic microspheres rapidly dissolve within the neutral pH of the lung tissue expediting the release of insulin absorbed into the systemic circulation. Administered with the inhaler device, this Technosphere® insulin technology facilitates attainment of peak levels within 15 minutes of administration and median time to maximum effect around 53 minutes. Although the onset of action is similar to that of rapid-acting insulin, the duration of action of Afrezza® is much shorter with a half-life of 28 to 39 minutes and return to baseline insulin levels achieved within approximately 180 minutes. Metabolism and elimination are identical to regular human insulin. The pharmacokinetic profile more closely resembles prandial insulin release in non-diabetic subjects and may help minimize post-prandial hypoglycemia.3 Additionally, data suggest that Technosphere® insulin creates greater suppression in endogenous glucose production earlier and more efficiently than regular insulin, rapid-acting insulin, or Exubera®.5,6 The mechanism of action is identical to that of endogenous insulin; Afrezza® stimulates glucose uptake in peripheral tissues, inhibits hepatic glucose production, lipolysis and proteolysis, and promotes protein synthesis.2

Dosing and storage

Afrezza® should be dosed at the start of each meal. The starting dose is based on the patient’s insulin use history (see Table 1).2 For patients using pre-mixed insulin, the manufacturer recommends dividing the total daily pre-mixed insulin dose in half, then administering the half dose equally among the 3 meals of the day using the conversion in Table 1. The other half dose should be administered as an injected basal insulin.

Afrezza® is available in single cartridges of 2 different strengths, 4 units (blue) and 8 units (green), to be administered in the Afrezza® inhaler, a breath-powered device.2 Instructions for determining the appropriate number of cartridges based on the required Afrezza® dosage are in Table 1.

Table 1: Afrezza® dosing conversion table.2

<table>
<thead>
<tr>
<th>Injected mealtime insulin dose</th>
<th>Afrezza® dose</th>
<th>Number of 4-unit (blue) cartridges needed</th>
<th>Number of 8-unit (green) cartridges needed</th>
<th>Total number of cartridges needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-naïve</td>
<td>4 units</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>≤4 units</td>
<td>4 units</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Afrezza® cartridges are supplied in blister strips, packaged in a foil laminate.2 Each blister strip pocket contains 3 cartridges with a total of 5 blister strips per card (15 cartridges per card). Two cards are packaged in the foil
laminate (30 cartridges per foil package). When not in use, the foil packages require refrigeration. Further storage recommendations may be found in Table 2.

Table 2: Storage of Afrezza®

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Storage</th>
<th>Discard after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sealed foil packages</td>
<td>36-46°F (2-8°C)</td>
<td>Expiration date</td>
</tr>
<tr>
<td><strong>Not in use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sealed cartridge strips</td>
<td>Room temperature</td>
<td>10 days</td>
</tr>
<tr>
<td>Opened cartridge strips</td>
<td>Room temperature</td>
<td>3 days</td>
</tr>
<tr>
<td>Inhaler</td>
<td>Room temperature</td>
<td>15 days</td>
</tr>
<tr>
<td><strong>In use</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Safety

Warnings and precautions

Afrezza® carries a boxed warning and is contraindicated in patients with chronic lung disease, including asthma or chronic obstructive pulmonary disease (COPD), due to risk of acute bronchospasm. Accordingly, the FDA has required a risk evaluation and mitigation strategy (REMS), through which the manufacturer must inform healthcare professionals regarding the serious risk of acute bronchospasm in this patient population. Clinical trials have shown a decrease in forced expiratory volume in 1 second (FEV1) among patients without chronic lung disease with use of Afrezza® over 2 years. Thus, prior to initiating therapy, the manufacturer recommends conducting spirometry tests to assess pulmonary function and the potential for pulmonary disease. Pulmonary tests should be repeated after 6 months of therapy and annually thereafter. Patients who develop pulmonary symptoms such as wheezing, shortness of breath, recurrent cough and bronchospasm should be monitored more frequently. Afrezza® should be discontinued if ≥20% decline in FEV1 is observed from baseline. To date, no definitive data exist with regards to lung cancer risk and Afrezza®; the potential benefits and risks should be assessed in patients with history of lung cancer or those who smoke.

Adverse reactions

As with injectable insulin, the most common side effect of Afrezza® is hypoglycemia. Severe hypoglycemia has been observed in 5.1% of patients with type 2 diabetes and non-severe hypoglycemia reported in 67% of these patients. Because Afrezza® is ultra-rapid-acting, the timing of hypoglycemia can be immediate, but symptomology can differ between patients with established disease and those newly diagnosed. Changes in meal timing or content, physical activity, and medications all influence risk of hypoglycemia.

In addition to hypoglycemia, other side effects, including diabetic ketoacidosis, hypokalemia, and heart failure (when used in combination with thiazolidinediones) have been reported with Afrezza®. Those reported most commonly in patients with type 2 diabetes mellitus were cough (25.6%), throat pain (4.4%), headache (3.1%), diarrhea (2.7%), productive cough (2.2%), fatigue (2.0%), and nausea (2.0%). Patients with type 1 diabetes mellitus experienced cough (29.4%), throat pain (5.5%), headache (4.7%), decreased pulmonary function (2.8%), bronchitis (2.5%), and urinary tract infection (2.3%).
Drug interactions

Patients using the following medications concurrently with Afrezza® may require more frequent glucose monitoring and dose adjustment as these medications may increase risk for hypoglycemia: antidiabetic agents, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs, and sulfonamide antibiotics.2

Medications that may decrease efficacy of Afrezza® include second generation antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, protease inhibitors, somatropin, sympathomimetics, and thyroid hormone.2 Increased glucose monitoring and dose adjustment may be warranted when Afrezza® is co-administered with these medications.

Efficacy

The safety and efficacy of Afrezza® have been evaluated in patients with type 1 diabetes and patients with type 2 diabetes. The original MedTone inhaler was used during initial clinical trials but was later replaced with the Gen2 inhaler intended for final marketing. The results of 2 pivotal phase 3 trials involving the Gen2 inhaler are outlined below.

Type 1 diabetes

Study 171 (MKC-TI-171) was a 24-week, open-label trial in which investigators sought to demonstrate non-inferiority of Afrezza® to insulin aspart in combination with basal insulin in patients with type 1 diabetes.4,7 The investigators included adult patients with diagnosis of type 1 diabetes at least 12 months prior to enrollment and on a stable basal/bolus regimen for at least 3 months with glycosylated hemoglobin (HbA1c) ≥7.5% and ≤10.0% and c-peptide ≤0.30 pmol/mL; patients were also non-smoking within 6 months prior. Significant exclusion criteria included ≥2 episodes of unexplained hypoglycemia within the previous 3 months, poor diabetic control requiring hospitalization or emergency room visit within 6 months, and history of pulmonary disease (e.g., COPD, asthma), active respiratory disease, and severe complications of diabetes (e.g., renal failure). Eligible patients were given insulin aspart and maintained on their pre-trial basal insulin for a 4-week run-in period to optimize their fasting blood glucose (FBG) to 100 to 120 mg/dL. Patients who achieved a FBG of <180 mg/dL after the 4-week run-in were then randomized to either Afrezza® (n=174) at an equivalent insulin aspart dose (10 units Afrezza: 4 units aspart) or insulin aspart (n=170) with each meal. Doses were titrated based on glycemic goals for 12 weeks then maintained for the remaining 12 weeks. The primary endpoint was change in HbA1c from baseline to study completion. Secondary endpoints were HbA1c goal attainment and changes in FBG and weight.

A total of 344 patients were assessed in Study 171 (Afrezza® n=174; aspart n=170).4 Baseline demographics were well-matched between the 2 groups. Overall, there were more females than males (56% female); the mean age was 38 years, and the majority (95%) were Caucasian. The mean baseline HbA1c was 8.0%. Basal insulin doses remained relatively stable throughout the study. The mean daily basal insulin dose by week 24 was 37.1 units and 31.6 units in Afrezza® and the insulin aspart arm, respectively. The overall mean daily prandial insulin dose was 102.7 units in the Afrezza® group and 25.5 units in the insulin aspart group.
At 24 weeks, the investigators observed non-inferiority of Afrezza® compared to insulin aspart with mean changes in HbA1c of -0.21% and -0.40%, respectively (treatment difference 0.19%; 95% confidence interval [CI]: 0.02 to 0.36, p=0.016). A total of 32 (18.3%) subjects in the Afrezza® arm achieved HbA1c <7% compared to 30.7% in the insulin aspart arm (odds ratio [OR] 0.449; 95% CI: 0.23 to 0.86, p=0.0158). A statistically significant change in FBG was observed in the Afrezza® group (-25.27 mg/dL) compared to the insulin aspart arm (+10.15 mg/dL) with a treatment difference of -35.42 mg/dL (95% CI: -56.25 to -14.59, p=0.0009). Patients did experience lower pre- and post- meal glucose excursions on both treatments when compared to baseline. Subjects treated with Afrezza® lost weight (-0.39 kg) whereas subjects receiving insulin aspart gained weight (0.93 kg); this was statistically significant (treatment difference -1.32 kg; 95% CI [-2.33 to -0.31], p=0.0102).

More patients withdrew from the Afrezza® arm (25%) than the insulin aspart arm (11%), citing adverse events as the most common reason for discontinuation. Hypoglycemia was the most common adverse event reported in this study. The total number of hypoglycemic events was higher in the insulin aspart arm (99.4%) versus Afrezza® (96.0%; p=0.0672). Of these events 29.2% were categorized as severe (BG <36 mg/dL) for the insulin aspart group compared to 18.4% in the Afrezza® group (p=0.0156). No serious cardiovascular events were reported, and the most common non-hypoglycemic event reported was cough (~30%).

Type 2 diabetes

Study 175 (MKC-TI-175) was a 24-week, double-blind trial comparing the efficacy of Afrezza® to placebo in patients with type 2 diabetes poorly controlled on oral antidiabetic drugs (OADs). Investigators included adult patients diagnosed with type 2 diabetes ≥12 months prior to enrollment, with HbA1C ≥7.5% and ≤10.0% on stable doses of metformin only or ≥2 OADs, and insulin-naïve. Other inclusion criteria were non-smoking for 6 months prior to the study and pulmonary function requirements (e.g., forced vital capacity [FVC] and FEV1 ≥70%, predicted). Subjects were excluded if they had significant pulmonary disease, severe complications from diabetes, renal dysfunction, significant cardiovascular dysfunction, previous use of amiodarone, treatment with glucagon-like peptide-1 (GLP-1) agonists, thiazolidinediones or weight-loss drugs, history of venous thromboembolism within 12 months, or recent blood transfusion. Subjects continued their pre-study OAD during a 6-week run-in period; those with HbA1c <7.5% after the run-in period were excluded from randomization. Qualifying patients were randomized to receive either Afrezza®, 10 units with meals, or an inhaled placebo. The primary endpoint was mean change in HbA1c from baseline to study completion. Secondary endpoints included HbA1c goal attainment and FBG and weight changes.

A total of 328 patients were analyzed in Study 175 (n=164 in both arms). Like Study 171, there were slightly more women than men in study 175 (56% women), and the majority of the study participants were Caucasian (>85%). The mean age was 56 years and baseline HbA1c was 8.3%. At 24 weeks, investigators observed a significant difference between groups in mean change in HbA1c, favoring Afrezza® (-0.82% Afrezza® vs. -0.42% placebo, treatment difference -0.40%; 95% CI: -0.57 to -0.23). A total of 37.7% of subjects in the Afrezza® arm achieved HbA1c <7% compared to 19.0% in the placebo group (OR 2.7; 95% CI: 1.55 to 4.80, p=0.0005). A greater change from baseline in FBG was observed in the Afrezza® group (-11.20 mg/dL) vs. placebo (-3.78 mg/dL), but this was not statistically significant (treatment difference 7.42 mg/dL; 95% CI: -18.03 to 3.18). Subjects receiving Afrezza® experienced slight weight gain (+0.49 kg) compared to weight loss in the placebo group (-1.13 kg; treatment difference 1.62 kg; 95% CI: 0.90 to 2.34).
Hypoglycemia was reported in 67.8% of patients treated with Afrezza® versus 30.7%, which was statistically significant (p<0.0001); of these events, 5.1% and 1.7% were categorized as severe for the active and placebo group, respectively. Sub-group analyses of patients taking metformin and Afrezza® versus metformin and a sulfonylurea showed no substantial difference in hypoglycemic event rates between the 2 groups.

Discussion

The phase 3 trials described above effectively demonstrate the safety and efficacy of Afrezza®,. In Study 171, involving patients with type 1 diabetes, the HbA1c lowering-effect was not as robust in the Afrezza® group, but this may be offset by the lower incidence of severe hypoglycemia. Interestingly, FBG was significantly lower in the Afrezza® arm, though this could be attributed to the higher average basal insulin dose. In Study 175, insulin-naïve patients with type 2 diabetes experienced a significant HbA1c reduction with Afrezza® added to OAD compared to OAD therapy plus placebo. However, these patients also experienced weight gain and a higher frequency of hypoglycemia compared to patients in the placebo group. Of note, the non-invasive administration of an inhaled insulin may provide greater adherence for patients who frequently miss their subcutaneous prandial insulin dose, resulting in better overall HbA1c control; adherence was not addressed in either study.

It remains to be seen whether Afrezza® will be a successful addition to the insulin marketplace. MannKind Corporation recently announced its plans to partner with Sanofi to develop and commercialize Afrezza®, which is slated to hit the US market as early as 2015. Still, Afrezza® has a long road ahead. As a condition of approval, the FDA is mandating 4 post-marketing studies, evaluating its use in pediatric patients and assessing cardiovascular risks and long term effects on pulmonary function, and completion of 2 pharmacokinetic/dynamic studies. The manufacturer will also have to reckon with the lingering question of increased lung cancer risk. While Afrezza® appears to have clear advantages relative to Exubera®, patient and provider buy-in will ultimately dictate its success.

References

Olmesartan: Does it Truly Increase the Risk of Cardiovascular-Related Death in Diabetics?

Jessica Beyer, PharmD

In June of 2014, the Food and Drug Administration (FDA) released a safety announcement with regard to 2 studies reporting an increased risk of death related to cardiovascular events in diabetic patients taking olmesartan. This announcement came after nearly 4 years of follow-up cohort studies and data analyses conducted by the FDA.

The 2 studies which sparked the initial investigation of olmesartan by the FDA were the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT). These studies are outlined in Table 1. ROADMAP, on a large scale, and ORIENT, on a smaller scale, sought to determine the effects of olmesartan on delaying the onset or progression of nephropathy in patients with diabetes. To the surprise of the investigators in both trials, there were significant increases in the occurrence of cardiovascular-related death, a secondary endpoint, in diabetic patients taking olmesartan. This was an unexpected outcome due to the demonstration of beneficial cardiovascular effects of angiotensin receptor blockers (ARBs) in widely accepted studies.1

ROADMAP2 demonstrated a statistically significant delay in the onset of microalbuminuria in patients taking olmesartan (hazard ratio [HR] 0.77, 95% confidence interval [CI]: 0.63 to 0.94). However, there was a statistically significant increase in the number of fatal cardiovascular events in patients taking olmesartan vs. placebo (see Table 1). Of note, the total number of cardiovascular events was similar between groups (4.3% olmesartan vs. 4.2% placebo). Upon further examination, the majority of fatal cases were caused by myocardial infarction (MI; n=5 vs. n=0) and sudden cardiac death (n=7 vs. n=1). Also, the majority of deaths in the olmesartan and placebo arms combined (12 of 18) occurred in patients with pre-existing coronary heart disease. The study investigators concluded these results may be due to chance because of the infrequency of events. They also hypothesized that in diabetic patients with pre-existing coronary heart disease, olmesartan may cause an excessive reduction in blood pressure leading to the potential for an increased risk of death.
### Table 1. Summary of cardiovascular outcomes from selected olmesartan studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design, Duration</th>
<th>Enrollment</th>
<th>Treatment Arms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROADMAP²</td>
<td>R, DB, MC trial&lt;br&gt;Median 3.2 years</td>
<td>4,447 patients in Europe, aged 18 to 75 years, with type 2 diabetes</td>
<td>Olm 40 mg daily&lt;br&gt;Placebo</td>
<td>Fatal CV events:&lt;br&gt;- 15 patients (0.7%) olm vs. 3 patients (0.1%) placebo&lt;br&gt;&lt;br&gt;<strong>HR 4.94, 95% CI 1.43 to 17.06</strong></td>
</tr>
<tr>
<td>ORIENT³</td>
<td>R, MC trial&lt;br&gt;Mean 3.2 years</td>
<td>577 patients in Japan and Hong Kong, aged 30 to 70 years with type 2 diabetes</td>
<td>Olm 10 to 40 mg daily&lt;br&gt;Placebo</td>
<td>Incidence of CV-related death:&lt;br&gt;- 10 patients (3.5%) olm vs. 3 patients (1.1%) placebo&lt;br&gt;&lt;br&gt;<strong>HR 3.38, 95% CI 0.93 to 12.29</strong></td>
</tr>
<tr>
<td>Graham 2014⁴</td>
<td>Retrospective cohort study&lt;br&gt;Mean study drug use 130 days</td>
<td>882,727 patients enrolled in Medicare, with or without diabetes, with ≥1 ARB prescription from 2007 to 2010</td>
<td>Olm 10 to 40 mg daily&lt;br&gt;Other ARB (candesartan, irbesartan, losartan, telmisartan, valsartan)</td>
<td>Increased mortality in diabetic subgroup taking high-dose (40 mg) olm vs any other ARB for ≥6 months:&lt;br&gt;- <strong>HR 2.03, 95% CI 1.09 to 3.75</strong>&lt;br&gt;Decreased mortality in non-diabetic patients taking high-dose olm vs any other ARB during first 6 months:&lt;br&gt;- <strong>HR 0.72, 95% CI 0.55 to 0.96</strong></td>
</tr>
<tr>
<td>Zhou 2014⁵</td>
<td>Retrospective cohort study&lt;br&gt;Mean 1.1 to 1.2 years</td>
<td>58,617 patients in UK, aged 40 to 95 years, with or without diabetes, with no ACE-I/ARB use in preceding 6 months</td>
<td>Olm 10 to 40 mg daily&lt;br&gt;Any other ARB (ARBs not specified)</td>
<td>Subgroup analysis of high-dose olm vs. high-dose other ARB:&lt;br&gt;- AMI: adjusted <strong>HR 3.09, 95% CI 0.94 to 10.13</strong>&lt;br&gt;- Stroke: adjusted <strong>HR 1.94, 95% CI 0.46 to 8.11</strong>&lt;br&gt;- Death: adjusted <strong>HR 2.03, 95% CI 0.74 to 5.61</strong>&lt;br&gt;Subgroup analysis of diabetics (6% [18/301] high-dose olm vs. 11.3% [800/7105] high-dose other ARB):&lt;br&gt;- No events in olm&lt;br&gt;- Events in other ARB:&lt;br&gt;- AMI: 5, stroke: 3, death: 17</td>
</tr>
<tr>
<td>Walker 2014⁶</td>
<td>Retrospective cohort study&lt;br&gt;Mean 8.1 to 9.5 months</td>
<td>254,971 patients in US, aged ≥20 years, with or without diabetes, with ≥1 claim for olm, another ARB, or ACE-I between 2002 and 2009; no prior use of ARB</td>
<td>Olm 10 to 40 mg daily&lt;br&gt;Any other ARB (ARBs not specified)&lt;br&gt;ACE-I (ACE-I not specified)</td>
<td>Sudden cardiac death non-diabetics, no prior use of ARB and ACE-I:&lt;br&gt;- Olm vs. ARB: 14 vs. 32 patients&lt;br&gt;- Olm vs. ACE-I: 13 vs. 42 patients&lt;br&gt;&lt;br&gt;<strong>HR 0.9, 95% CI 0.5 to 1.6</strong>&lt;br&gt;- Olm vs. ACE-I: 3 vs. 3 patients&lt;br&gt;- Olm vs ACE-I: 3 vs. 3 patients&lt;br&gt;&lt;br&gt;<strong>HR 2.1, 95% CI 0.4 to 11.7</strong>&lt;br&gt;- Olm vs ACE-I: 3 vs. 3 patients&lt;br&gt;&lt;br&gt;<strong>HR 2.0, 95% CI 0.4 to 10.7</strong></td>
</tr>
</tbody>
</table>

R=randomized, DB=double-blind, MC=multicenter, olm=olmesartan, CV=cardiovascular, HR=hazard ratio, CI=confidence interval, ARB=angiotensin receptor blocker, ACE-I=angiotensin converting enzyme inhibitor, UK=United Kingdom, US=United States, AMI=acute myocardial infarction
In ORIENT, the primary endpoint was occurrence of doubling of serum creatinine; the investigators did not observe a significant difference between groups (41.1% olmesartan vs. 45.4% placebo, p=0.791). While not statistically significant, there was a higher incidence of cardiovascular-related death in the olmesartan group versus the placebo group (see Table 1). However, like ROADMAP, the occurrence of cardiovascular events (18 olmesartan vs. 21 placebo) and all-cause mortality (19 olmesartan vs. 20 placebo) was similar between groups. Ultimately, the trial was insufficiently powered to determine an effect of olmesartan on cardiovascular outcomes. Additionally, the investigators determined a 2-fold higher proportion of patients with cardiovascular disease in the olmesartan group vs. placebo group. This makes it difficult to determine if the increase in mortality was due to olmesartan or the increased number of patients with pre-existing cardiovascular disease.

In addition to reviewing the results of ROADMAP and ORIENT, the FDA reviewed several cohort studies to determine if increased risk of cardiovascular-related death in patients with diabetes is a class effect of ARBs. The first was a new-user cohort study of Medicare beneficiaries, comparing use of olmesartan to use of any other ARB. Results from this study indicated a statistically significant increase in mortality in diabetic patients taking high-dose olmesartan (see Table 1). Conversely, it demonstrated a statistically significant decrease in mortality in non-diabetic patients taking high-dose olmesartan. These results call into question the validity of this study as it seems unlikely for an exposure to be associated with increased cardiovascular risk in 1 group and decreased cardiovascular risk in another.

In another cohort study, conducted in the United Kingdom (UK), Zhou et al compared patients who initiated olmesartan with those who initiated another ARB to evaluate the risk of acute MI, stroke, and death. The study included patients using high-dose olmesartan or other ARBs and involved a subgroup of diabetic patients. Zhou et al did not find a statistically significant difference in the risk for acute MI, stroke, or all-cause mortality among diabetic patients taking olmesartan versus any other ARB. It is important to note, however, the number of diabetic patients receiving high-dose olmesartan was small and may not have represented the large numbers of diabetic patients taking high-dose olmesartan, as observed in the ROADMAP trial.

The manufacturer of Benicar® (olmesartan), Daiichi-Sankyo, conducted a cohort study evaluating cardiovascular mortality among olmesartan-, other ARBs-, and angiotensin-converting enzyme inhibitors (ACE-I)-users. The results of the study showed no statistically significant differences in the relative risk for sudden cardiac death when comparing olmesartan to other ARBs and olmesartan to ACE-Is in patients without diabetes. Similarly, there were no statistically significant differences in the relative risk for sudden cardiac death in diabetic patients taking olmesartan, other ARBs, or an ACE-I. However, this study failed to assess the effects of high-dose olmesartan.

In addition to the cohort study, Daiichi-Sankyo conducted an unpublished meta-analysis including placebo- and active-controlled studies of olmesartan. When ROADMAP and ORIENT were removed from the analysis, the investigators observed no significant difference between olmesartan and comparator groups for cardiovascular death or all-cause mortality (results not specified).

In summary, several studies have been conducted to evaluate whether olmesartan increases the risk of cardiac death in diabetic patients; however, the data are inconclusive. The Medicare study results support the theory that olmesartan increases the risk of cardiac death; however, the reduction of cardiac death in non-diabetic patients suggests that these results may be due to chance. While the results of the UK and manufacturer studies appear
to refute the results of the ROADMAP and ORIENT trials, the former 2 studies did not effectively evaluate the risk of cardiac death with high-dose olmesartan in diabetic patients.5,6

After thoroughly reviewing the available literature, the FDA made the announcement that it “found no clear evidence of increased cardiovascular risks associated with the use of the blood pressure medication olmesartan in diabetic patients.”1 While their recommendations for the use of olmesartan remain unchanged, the FDA is requiring information from some of the studies to be included in olmesartan-containing product labels.

Additionally, prescribers should note that the cardiovascular risks associated with untreated hypertension may substantially outweigh those of high-dose olmesartan. Thus, prescribers are advised to heed the FDA recommendations regarding use of olmesartan.

References


Naloxone: Increasing Accessibility to Save Lives in the Battle Against Substance Abuse

Lisa Garza, PharmD

Background

Substance abuse is a growing problem. In 2010, deaths attributed to opioid overdoses reached almost 17,000, which is near the number of deaths attributed to motor vehicle accidents.1 Fatal drug overdose has become a leading cause of preventable death over the last decade with the associated rate doubling from 7 to 14 per 100,000 people according to the Centers for Disease Control and Prevention (CDC). The rise in overdose-related deaths has led some experts to refer to substance abuse as an epidemic.2

Reducing morbidity and mortality associated with substance abuse will require a comprehensive plan. The Office of National Drug Control Policy has developed a multi-pronged approach that includes the following
strategies: educating providers on appropriate prescribing practices, increasing monitoring of controlled medications, increasing proper medication disposal, and improving access to opioid overdose reversal agents, specifically naloxone. Pharmacists are in a prime position to contribute to these efforts, particularly in dispensing naloxone.

Naloxone is an opioid antagonist that works primarily on the mu receptors in the brain to reverse opioid-induced effects. The drug is available as a solution for intravenous and intramuscular injection. In addition, in April 2014, the Food and Drug Administration (FDA) approved an auto-injector (Evzio™) for intramuscular or subcutaneous use. An atomizer device has been developed for intranasal administration; however, this device is not currently FDA-approved. The onset of action is 2 to 5 minutes for the intramuscular form and 8 to 13 minutes for the intranasal form. The effects last approximately 30 to 120 minutes depending on the formulation. This duration is shorter than that of most opioids; thus, repeated doses are usually necessary. Due to the abrupt antagonism of opioid effects, administration of naloxone in opioid-dependent patients may result in rapid onset of withdrawal symptoms, such as tachycardia, agitation, nausea, vomiting, diarrhea, diaphoresis, and tremor. Other adverse effects, including hypotension, hypertension, ventricular tachycardia/fibrillation, dyspnea, pulmonary edema, and cardiac arrest, have been reported in the post-operative setting.

Many states, including California, Kentucky, Rhode Island, North Carolina, and Washington, have passed legislation allowing pharmacies to dispense naloxone without a prescription. Data have been collected to determine if increasing layperson access to naloxone impacts opioid-related fatalities. In Massachusetts, a study assessing the effects of opioid overdose education and naloxone distribution (OEND) programs demonstrated that these programs were feasible and reduced opioid overdose deaths. According to the CDC, between 1996 and 2010, >50,000 potential bystanders received opioid overdose education and naloxone distribution training, resulting in >10,000 opioid overdose reversals with naloxone. These findings suggest that OEND is effective for management of opioid overdosage and that it may reduce opioid-related death rates.

**Overview**

In June 2014, New York State Governor Andrew Cuomo signed bill S6477/A8637, expanding access to naloxone. S6477/A8637 took effect immediately after signing and emergency regulations were released in August. The law authorizes healthcare professionals to prescribe, dispense, and distribute naloxone via a non-patient specific order to persons at risk of opioid overdose, concerned friends or family members, or individuals positioned to assist those at risk of opioid overdosage. The law also discusses legal protection for parties involved in stocking and distributing naloxone and requires the state to publish data on fatal opioid overdoses annually for the next 3 years.

Under this new law, naloxone may be distributed to pharmacies as well as at off-site, registered programs. This is a drastic improvement in accessibility from previous legislation.
Review of legislation

Over the last decade, New York lawmakers have been working to increase availability and usage of naloxone by laypersons. In 2005, the state authorized non-medical personnel to administer naloxone; however, the assistance of emergency medical personnel was still required. This presented issues in the form of under-reporting and negligence, due to fear of prosecution associated with illegal activity (e.g., illicit drug use). In response, a Good Samaritan Law was passed in 2011, granting immunity to individuals contacting emergency personnel regarding a suspected overdose, despite potential involvement in illegal activity (e.g., possession of illicit drugs/paraphernalia, underage drinking).

These laws expanded access to naloxone and improved utilization of emergency services by reducing consequences for bystanders. However, access to naloxone was still an issue. Parties interested in obtaining naloxone were required to enroll in state-certified opioid overdose prevention programs, many of which are located in metropolitan areas. This could present a barrier to individuals residing in rural areas. Thus, the recent allowance for naloxone distribution to pharmacies and direct dispensing to laypersons is significant.

The role of pharmacy

With the passing of these laws in New York and similar laws in other states, there are new opportunities for pharmacists to collaborate with local offices and programs to assist in the provision of naloxone to members of the community. Multi-state retail pharmacies such as Walgreens and CVS are beginning to participate in naloxone distribution. This is especially beneficial for more rural and suburban communities that do not have access to resources offered in major metropolitan areas.

In August, emergency rules and regulations were passed to provide guidance on implementation of the June 2014 law. Most of the rules and regulations are related to opioid overdose prevention programs; notably, pharmacies are not required to register as a program in order to dispense naloxone. As the law and regulations are written, a patient will be able to present to a pharmacy, with or without a prescription, and request naloxone. If he/she does not have a prescription, the pharmacy will need a standing order to dispense the product.

At this time, New York State requirements for documentation, reporting, and dispensing naloxone, as well as counseling/training recipients, are being further discussed for implementation. Some pharmacies in other states dispense kits with 2 doses of 0.4 mg naloxone, for intramuscular or intranasal administration, after the recipient has been adequately trained. Costs vary by location and insurance coverage, but the cost of most kits with injectable and intranasal dosage forms is below $50; in contrast, the average wholesale price of Evzio™ (2 auto-injectors) is $690. Kits typically contain a leaflet of important information including symptoms of opioid
overdose and recommended procedure (e.g., contacting emergency personnel, drug administration). Figure 1 represents an example of a naloxone prescription form and instructions for use.

Pharmacists should be prepared to provide counseling on naloxone, especially if employed at a pharmacy dispensing these products. Additional counseling on opioid overdosage, such as recognition and avoidance, may also be addressed. The example illustrated in Figure 1 includes basic counseling points. More information, including videos, can be found at www.prescribetoprevent.org or www.stopoverdose.org. Registered opioid overdose prevention program locations can be found at www.overdosepreventionalliance.org.

Figure 1. Example naloxone prescription form and instructions for use.¹⁰

Conclusion

Naloxone can rapidly and safely reverse an overdose. Reducing opioid-related deaths is a serious and complicated public health issue that requires a multi-faceted approach. New York State has greatly improved
access to naloxone by passing S6477/A8637 into law, but we still do not know exactly how this will be implemented in pharmacies. The full benefits and effects of these efforts in New York and other states remains to be seen and will become evident as related research and experience continues to grow.

References


Hepatitis C Treatment Guideline Update 2013/2014
Holly Hamilton, PharmD

With the recent approval of 2 new medications for treatment of chronic hepatitis C (HCV) infection, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA), in collaboration with the International Antiviral Society–USA (IAS–USA), have developed web-based guidance for HCV management.¹ Guidelines were previously released in 2009 with an update in 2011 for treatment of patients with HCV genotype 1, following the approval of boceprevir and telaprevir. In January 2014, these publications were replaced with a website allowing for ongoing updates, in an effort to provide healthcare professionals with timely recommendations. These updates include novel recommendations for use of the 2 new drugs, sofosbuvir (Sovaldi®) and simeprevir (OlysioTM), in various combinations with 2 established HCV medications, ribavirin and peginterferon alfa-2a (peginterferon). Notably, prior to the development and approval of sofosbuvir and simeprevir, ribavirin and peginterferon were considered the “gold standard” in HCV treatment.
The new recommendations support simplified treatment options with shorter durations of therapy and improved adverse event profiles, which are especially appealing to patients who have been unable to tolerate past therapies, did not previously qualify for treatment, or who have other barriers to HCV treatment.

An overview of the new guidance with a brief introduction to the 2 new HCV agents, sofosbuvir and simeprevir, is provided below.

**New drug overview: sofosbuvir**

Sofosbuvir (Sovaldi®) is an HCV nucleotide analog NS5B polymerase inhibitor and is the first available drug in its class.² Sofosbuvir was approved by the Food and Drug Administration (FDA) in 2013 for treatment of patients with HCV genotypes 1, 2, 3, or 4. Sofosbuvir acts by competing with the natural nucleotides found within the hepatocyte, utilized during viral replication. By competing with these nucleotides, the drug causes chain termination of the viral ribonucleic acid (RNA) on the primer strand. Because of this chain termination, the viral replication process is halted.

Sofosbuvir is dosed at 400 mg once daily and can be taken with or without food.² The side effects of this medication are minimal. Patients should be educated on the risk of fatigue and headache, which have been reported at an incidence ≥20% when used in combination with ribavirin. When used in combination with peginterferon and ribavirin, other common side effects that have been reported include insomnia, nausea, and anemia, but these effects are more associated with peginterferon and ribavirin.

With regard to drug-drug interactions, the only reported interaction of potential clinical significance is a decrease in sofosbuvir levels in the body when used with potent P-glycoprotein (P-gp) inducers, such as phenytoin, rifampin, and St. John’s Wort.² Co-administration of these drugs can lead to a reduced therapeutic effect of the sofosbuvir; thus, the manufacturer recommends that potent P-gp inducers be avoided in combination with this medication.

**New drug overview: simeprevir**

Simeprevir (Olysio™) is an HCV NS3/4A protease inhibitor and is the third approved drug in this class.³ The drug was approved by the FDA in 2013 for treatment of patients with HCV genotype 1. Simeprevir acts by directly inhibiting the NS3/4A protease enzyme, which is necessary for HCV replication. When this enzyme is inactivated, the cleaving of the immature and non-infectious viral protein is halted, preventing production of a new, viable virus.

The recommended dose of simeprevir is 150 mg daily; the drug must be taken with food.³ The side effects of this medication, as with sofosbuvir, are minimal; however, patients taking simeprevir should be educated on the
risk of photosensitivity, rash, pruritis, and nausea. Standard sun protection barriers and behaviors should be applied during therapy.

With regard to drug-drug interactions, co-administration with drugs that are moderate or strong inducers or inhibitors of cytochrome P450 (CYP) 3A may significantly alter plasma simeprevir concentrations.\(^3\) Caution is advised when using simeprevir with these agents.

**When and in whom HCV treatment should be initiated**

Treatment for chronic HCV is of the highest priority for individuals with advanced fibrosis (METAVIR stage 3), compensated cirrhosis (METAVIR stage 4), liver transplants, or severe extrahepatic manifestations of hepatitis C.\(^1\) The goal of HCV treatment is to reduce mortality and liver-related adverse events by achieving virological cure. Due to a limitation on resources, it is important that HCV treatment be prioritized to those individuals who will receive the most benefit. This is an issue of considerable controversy; in the United States, HCV treatment is highly costly, and there is debate regarding the manufacturer pricing and restrictions implemented by third party payers. HCV treatment is considered effective when a sustained virologic response (SVR) is achieved. SVR is defined as the continued absence of detectable HCV RNA \(\geq 12\) weeks after completion of therapy. This is an update from previous recommendations that defined SVR as an absence of detectable HCV RNA \(\geq 24\) weeks after completion of therapy. This change occurred because there is substantial evidence to suggest the majority of patients who relapse will have a detectable HCV RNA within 12 weeks of treatment completion.\(^4\) Patients who do achieve SVR will always have HCV antibodies but will no longer have a detectable viral load. Benefits of achieving SVR include reductions in liver inflammation, liver fibrosis, mortality, and symptoms related to chronic HCV infection.

**Treatment – mono infection only**

When initiating drug treatment, the decision on which agents to use should be based on the patient’s HCV genotype. There are 6 HCV genotypes. Two of these HCV genotypes, 5 and 6, are not commonly observed in the United States and will likely be rarely encountered in practice; thus, this review will focus on the recommended treatment regimens for genotypes 1 through 4, both in treatment-naïve and treatment-experienced patients. These recommendations are outlined in Appendix 1 and Appendix 2. Recommendations for special populations (e.g., patients with human immunodeficiency virus [HIV] co-infection, renal impairment) and alternative regimens are available but excluded from this review.
**Treatment-naïve patients**

**Genotype 1**

Sofosbuvir + ribavirin + peginterferon should be administered for a duration of 12 weeks, unless the patient is ineligible to receive peginterferon.\(^1\) This recommendation was based on the results of the NEUTRINO trial, which showed an 89% SVR rate using this triple drug regimen in 291 treatment-naïve patients.\(^5\)

Of note, peginterferon is not easily tolerated; the drug has many side effects that could be intolerable for some patients.\(^6\) Common side effects of peginterferon include constitutional or flu-like symptoms such as fatigue, fever, and headache. Other reported side effects include an increased risk for serious or life-threatening neuropsychiatric disorders, such as depression. Caution is advised when using peginterferon in patients who have or have had any psychiatric disorders; a peginterferon-free regimen may be preferred in these patients. Other contraindications to peginterferon use include hepatic decompensation and certain autoimmune disorders (e.g., autoimmune hepatitis).

For those patients who are ineligible for peginterferon therapy, a regimen consisting of sofosbuvir + simeprevir with or without ribavirin should be administered for a duration of 12 weeks.\(^1\) This recommendation was based on preliminary results of the COSMOS trial, demonstrating SVR rates of 93% (without ribavirin) to 96% (with ribavirin) in patients using these regimens.\(^7\) Ribavirin should be used in combination with sofosbuvir and simeprevir in the absence of a Q80K mutation. The Q80K mutation decreases the activity of simeprevir in combination with peginterferon and ribavirin; therefore, testing for the Q80K polymorphism prior to administration of this combination is recommended. Notably, the Q80K mutation has not been shown to affect the efficacy of simeprevir used in combination with sofosbuvir.\(^1\)

**Genotype 2**

Sofosbuvir + ribavirin is recommended for a duration of 12 weeks.\(^1\) This recommendation was based on the results of 3 clinical trials: FISSION, POSITRON, and VALENCE. These studies determined that the use of sofosbuvir + ribavirin led to higher SVR than peginterferon + ribavirin with collective SVR rates of 94% vs. 78%.\(^1,5,6,10\)

**Genotype 3**

Sofosbuvir + ribavirin is recommended for a duration of 24 weeks.\(^1\) This recommendation was based on the results of several clinical trials, including VALENCE, FISSION, FUSION, and POSITRON. During these studies, investigators observed a 40% relapse rate in patients treated with this combination for 12 weeks. Initial SVR rates were higher in treatment-naïve patients compared to treatment-experienced patients (93% vs.
77%).\textsuperscript{1,5,6} Investigators determined that extending the duration of therapy may reduce the relapse rate – among treatment-naïve patients, extended therapy was associated with a reduction in relapse rate from 40% to 5%.

**Genotype 4**

Sofosbuvir + ribavirin + peginterferon is recommended for a duration of 12 weeks.\textsuperscript{1} This recommendation was derived from the results of the NEUTRINO trial, in which SVR was achieved by 96% of participants with genotype 4 (n=28).\textsuperscript{5} Compared to genotypes 1 through 3, genotype 4 is not as common; thus, there are limited data to guide treatment in this patient population. Current recommendations are based on the available data, but these recommendations may not be appropriate for all individuals with HCV genotype 4.

For patients who are ineligible for peginterferon therapy, sofosbuvir + ribavirin is recommended for a duration of 24 weeks.\textsuperscript{1} This recommendation was derived from a small study of Egyptian patients in the United States, in which 79% of patients achieved SVR at 12 weeks, and 100% achieved SVR at 24 weeks.\textsuperscript{7}

**Treatment-experienced patients**

When treating a patient who has previously received therapy for HCV, it is important to note that the response to treatment will be similar to that of treatment-naïve individuals if an undetectable viral load was achieved during the previous course of treatment. In patients with prior null response (individuals who never achieved an undetectable viral load), the treatment response is generally lower.\textsuperscript{1} Recommendations for patients who have not responded to therapy with peginterferon and ribavirin are outlined below.

**Genotype 1**

Sofosbuvir + simeprevir with or without ribavirin is recommended for a duration of 12 weeks.\textsuperscript{1} If the patient was previously treated with an HCV protease inhibitor (telaprevir or boceprevir), a regimen consisting of sofosbuvir for a duration of 12 weeks and ribavirin + peginterferon for a duration of 12 to 24 weeks is recommended. These recommendations are based on preliminary results from the COSMOS trial, which included 80 null responders with METAVIR stage 0 to 2 fibrosis. Of these individuals, 79% to 96% achieved SVR.\textsuperscript{1,9} Among the 22 null responders with METAVIR stage 3 or 4 fibrosis, SVR was observed in 93% (14/15) of the ribavirin arm and 100% (7/7) of the ribavirin-free arm.

**Genotype 2**

Sofosbuvir + ribavirin is recommended for a duration of 12 weeks.\textsuperscript{1} High SVR rates have been demonstrated in patients without cirrhosis at 12 weeks. However the FUSION study indicated that extension of therapy would be beneficial in patients with cirrhosis.\textsuperscript{6} A comparison of those receiving 16 weeks of therapy vs. 12 weeks of
therapy indicated that the proportion of patients achieving SVR was higher with extended therapy (78% and 60%, respectively), however in the VALENCE study, investigators observed high rates of SVR at 12 weeks in cirrhotic patients. Based on these conflicting results, extended duration of treatment to 16 weeks may be advised in patients of this genotype with cirrhosis.

**Genotype 3**

Sofosbuvir + ribavirin is recommended for a duration of 24 weeks. This recommendation is based on findings of the FUSION and VALENCE trials. In FUSION, investigators compared the effects of 12-week therapy to 16-week therapy in patients with genotypes 2 and 3. The majority (63%) of participants had HCV genotype 3. Among these patients, SVR was achieved by 30% at 12 weeks and 62% at 16 weeks. Due to these findings, VALENCE investigators amended the study treatment period to 24 weeks in patients with HCV genotype 3. They observed an SVR rate of 79% among treatment-experienced patients with genotype 3.

**Genotype 4**

A regimen consisting of sofosbuvir + ribavirin + peginterferon for a duration of 12 weeks is recommended. As with treatment-naïve patients, the data are limited for this HCV genotype. This recommendation is based on results from the NEUTRINO trial, which enrolled a total of 24 treatment-experienced patients. Among these patients, 96% achieved SVR.

**HCV screening recommendations**

In addition to the recommended treatment regimens for HCV, providers are advised to review the HCV screening recommendations. By following these recommendations, individuals who are at high risk for HCV transmission can be identified and linked to care appropriately, which could lead to significant reductions in HCV transmission.

When counseling on HCV testing and treatment, patients should be informed that HCV is primarily transmitted through exposure to blood. HCV can also be transmitted vertically (from mother to child) and through any contaminated devices (e.g., lancets and blood glucometers). HCV may also be transmitted through sexual intercourse, although this is not as common as other sexually-transmitted diseases, such as HIV. The most important risk factor for HCV infection is injection drug use, which has been reported to account ≥60% of HCV infections in the United States.

HCV testing continues to be recommended for all individuals who were born between 1945 and 1965, regardless of HCV risk factors. Individuals born during this time period should be tested at least once in their lifetime. Additionally, 1-time testing should be performed in all persons with behaviors, exposures, and
conditions associated with an increased risk for HCV infection. Some examples of high-risk patient populations include intravenous (IV) drug users (current or ever, including individuals who injected only once), intranasal illicit drug users, individuals who are receiving or have received long-term hemodialysis, individuals who have received a tattoo in an unregulated setting, healthcare and public safety workers after possible exposure to HCV-infected blood, children born to HCV-infected women, certain transfusion or organ transplant recipients, individuals who were incarcerated, and individuals who are HIV-positive. For those individuals who participate in IV drug use or HIV-positive men who have unprotected sex with men, annual HCV testing is recommended. These recommendations are based on HCV prevalence in these specific populations.

**Summary**

The introduction of the 2 new HCV medications, sofosbuvir and simeprevir, offers patients and providers safer treatment options and allows for treatment regimens of shorter duration. Reported side effects of both medications are minimal compared to those of previous treatment options. Their efficacy, as defined by SVR, has been demonstrated in several trials, with high SVR rates observed among patients of varying stages of fibrosis, treatment exposure, and HCV genotype. These 2 agents provide a window into the future of HCV treatment; there are other new medications and combination products in development for this patient population. While these drugs represent an astonishing breakthrough in HCV treatment, efforts to prevent transmission should continue to be emphasized, through encouragement of HCV screening in patients at high risk.

**References**

Appendix 1. AASLD/IDSA/IAS-USA recommendations for treatment-naïve patients with HCV genotypes 1-4.¹

<table>
<thead>
<tr>
<th>Genotype</th>
<th>1st Line IFN-Eligible</th>
<th>1st Line IFN-Ineligible</th>
<th>Alternative IFN-Eligible</th>
<th>Alternative IFN-Ineligible</th>
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<tbody>
<tr>
<td>1</td>
<td>SOF + PEG/RBV x 12 wks</td>
<td>SOF + SMV ± RBV x 12 wks</td>
<td>SMV x 12 wks + PEG/RBV x 24 wks</td>
<td>SOF + RBV x 24 wks</td>
</tr>
<tr>
<td>2</td>
<td>SOF + RBV x 12 wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SOF + RBV x 24 wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SOF + PEG/RBV x 12 wks</td>
<td>SOF + RBV x 24 wks</td>
<td>SMV x 12 wks + PEG/RBV x 24 to 48 wks</td>
<td>SOF + RBV x 24 wks</td>
</tr>
</tbody>
</table>

IFN=interferon, SOF=sofosbuvir, PEG=peginterferon, RBV=ribavirin, SMV=simeprevir

Appendix 2. AASLD/IDSA/IAS-USA recommendations for treatment-experienced patients with HCV genotypes 1-4.¹

<table>
<thead>
<tr>
<th>Genotype</th>
<th>1st Line</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SOF + SMV ± RBV x 12 wks</td>
<td>SOF x 12 wks + PEG/RBV x 12 to 24 wks &lt;br&gt; OR &lt;br&gt; SMV x 12 wks + PEG/RBV x 48 wks &lt;br&gt; OR &lt;br&gt; SOF + RBV x 24 wks</td>
</tr>
<tr>
<td>2</td>
<td>SOF + RBV x 12 wks</td>
<td>SOF + PEG/RBV x 12 wks</td>
</tr>
<tr>
<td>3</td>
<td>SOF + RBV x 24 wks</td>
<td>SOF + PEG/RBV x 12 wks</td>
</tr>
<tr>
<td>4</td>
<td>SOF + PEG/RBV x 12 wks</td>
<td>SOF + RBV x 24 wks</td>
</tr>
</tbody>
</table>

SOF=sofosbuvir, SMV=simeprevir, RBV=ribavirin, PEG=peginterferon
Author Biographies

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Dr. Pignato received her Bachelor of Science degree in Chemistry and completed the Doctor of Pharmacy program at St. John Fisher. She is the current PGY-1 pharmacy practice resident at Buffalo Medical Group. Her professional interests include chronic disease state management, medication safety, teaching, and research. She plans to pursue a career in pharmacy academia with a clinical practice site in an ambulatory care setting.

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Dr. Garza graduated from Gonzaga University with a Bachelor of Arts in Chemistry and Biology and completed the Doctor of Pharmacy program at Washington State University College of Pharmacy. She is the current PGY-1 community pharmacy practice resident at the UB/Middleport Family Health Center. Dr. Garza has prior experience working in the community setting and has strong interests in independent community pharmacy, teaching, and professional engagement and leadership.

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Dr. Hamilton completed her undergraduate pre-pharmacy education at Purdue University and received her Doctor of Pharmacy degree from Sullivan University College of Pharmacy. Dr. Hamilton completed her PGY-1 community practice residency with Walgreens and Sullivan University in Louisville, Kentucky in 2014. Currently, she is the PGY-2 pharmacy practice resident in HIV/AIDS Pharmacotherapy at Erie County Medical Center. Dr. Hamilton has several years of experience in community pharmacy practice and has a strong interest in HIV Pharmacotherapy. She has plans to continue to practice in immunodeficiency services upon completion of her residency. Within her specialty, Dr. Hamilton has interests in HIV prevention and hopes to obtain a clinical position in an ambulatory care setting with teaching opportunities.

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