Abstract

Purpose

Current issues regarding biosimilar drug use are reviewed in a two-part article from the perspective of pharmacy practice.

Background

Statins are known to be safe, but some patients discontinue the therapy due to adverse effects. Given the clinical benefits of statin therapy, it is important to find different strategies to maintain its use. The aims of this systematic review were to summarize and critically appraise evidence of the efficacy, tolerability, and economic evaluation of non-daily statin administration in the past ten years.

Methods

Literature was searched through Cochrane, Embase, PubMed and Web of Science using relevant search terms. Studies of any size and design published between January 2007 and August 2017 were considered for the assessment of efficacy and tolerability. For economic evaluation, the search was repeated without restriction to the publication year to identify more relevant articles.

Results

All eleven studies, of which three were randomized controlled trials, supported the use of intermittent statin regimens to lower low-density lipoprotein (LDL) levels in patients with dyslipidemia. Most of the studies reported high tolerability to intermittent statin therapy, ranging from 72.5% to 100%. Economic analysis of four articles showed that the intermittent regimen is cost-saving in terms of cost per 1% LDL reduction.

Conclusion

Our systematic review of current evidence suggests that patients with dyslipidemia may reduce their LDL levels with intermittent statin administration. Non-daily administration has other benefits of improved tolerability and lower cost when compared to daily administration.

Keywords: hyperlipidemia; hypercholesterolemia; hydroxymethylglutaryl-coa reductase inhibitor; statins, intolerability, myopathy, non-daily statin, intermittent statin.

Introduction

Hydroxymethylglutaryl-coa (HMG-CoA) reductase inhibitors or statins, a therapeutic class of lipid-lowering medications, reduce plasma cholesterol levels by inhibiting HMG-CoA reductase in the cholesterol biosynthetic pathway. The American Heart Association (AHA) / American College of Cardiology (ACC) 2013 guidelines recommend an initiation of moderate to high intensity statins to reduce cardiovascular events, including myocardial infraction, stroke, and death.1 Although statins are generally known to be safe, some patients discontinue the therapy due to adverse effects, including myalgia, gastrointestinal symptoms, and hepatic enzyme elevation. In an analysis of 16,496 patients with dyslipidemia, the rate of withdrawal from the study due to adverse events was 3% for atorvastatin and 4% for other statins.2 Specifically, myalgia was reported in 1.9% of the patients on atorvastatin and 2% on other statins. Given the well-known clinical benefits of statin therapy, it is important to find different strategies to maintain its use.

In 2013, a systematic review by Keating et al. suggested that intermittent statin administration may be beneficial in lowering LDL.3 Of all the statins, rosuvastatin and atorvastatin were most commonly studied due to high potency and long half-life of 19 hours and 14 hours, respectively.4,5 However, the previously published systematic review3 was based on older evidence and did not include economic analysis. The aims of this systematic review were to summarize and critically appraise evidence of the efficacy, tolerability and economic evaluation of non-daily statin administration in the past ten years.

Methods

Search strategy and study selection

We searched literature using the following databases: Cochrane, Embase, PubMed and Web of Science. The controlled search terms and keywords used in the search were hydroxymethylglutaryl-coa reductase inhibitor, statin, drug administration schedule, side effect, intolerant, myalgia, cholesterol, hyperlipidemia, and hypercholesterolemia. The detailed search strategy was reported in Supplemental table 1.

Identified articles were initially screened for relevance to research question by title and abstract. Full text was retrieved for relevant studies and reviewed further for exclusion criteria (Figure 1).

Selection criteria

Studies of any size and design published between January 2007 to August 2017 were considered for eligibility. Inclusion criteria were studies that evaluated non-daily statin therapy for the treatment of dyslipidemia in adult
patients with or without a history of intolerance to statin therapy. Exclusion criteria were duplicates, reviews, news, commentaries, and articles that evaluated combination therapy. For the economic analysis, the search was not restricted to the publication year to identify more relevant studies.

**Data collection**

Data were collected from individual studies for publication year, study design, sample size, statin regimen, study duration, baseline LDL, age, LDL reduction, tolerability and adverse effects. For the cost analysis, data for publication year, study design, sample size, country, and cost reduction were collected.

### Table 1.

<table>
<thead>
<tr>
<th>Study [pub. year]</th>
<th>Design</th>
<th>Sample size (n)</th>
<th>Regimen</th>
<th>Study duration (months) [SD]</th>
<th>Baseline LDL (mg/dl) [SD]</th>
<th>Age (years) [SD]</th>
<th>% LDL reduction [SD]</th>
<th>% Tolerability</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promink 2012</td>
<td>RCT</td>
<td>40</td>
<td>Alternate day</td>
<td>7</td>
<td>154 [3.77]</td>
<td>52.8 [1.54]</td>
<td>38.37 p = NR</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Backers 2008</td>
<td>Retrospective cohort study</td>
<td>51</td>
<td>Alternate day</td>
<td>4.2 [0.9]</td>
<td>164.9 [31.2]</td>
<td>58.5 [10.5]</td>
<td>34.5 p &lt; 0.001</td>
<td>72.5</td>
<td>Myalgias, gastrointestinal complaints</td>
</tr>
<tr>
<td>Goldberg 2015</td>
<td>Retrospective cohort study</td>
<td>58</td>
<td>3 - 4 times a week</td>
<td>5</td>
<td>Intervention: 3.2 mg/d; 10 mg daily 2.2 [0.8]; 5 mg daily 2.2 [0.8]</td>
<td>Intervention: 6.2 mg/d; 10 mg daily, 577 [11]</td>
<td>34.4 [21.3] p &lt; 0.001</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Ghotas 2009</td>
<td>Prospective cohort study</td>
<td>100</td>
<td>3 - 5 times a week</td>
<td>75</td>
<td>182</td>
<td>60 [34 to 80]</td>
<td>44.6 p &lt; 0.0001</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mackie 2007</td>
<td>Case report</td>
<td>2</td>
<td>Mon - Wed - Fri</td>
<td>16</td>
<td>&lt; 130</td>
<td>NR</td>
<td>20.48 p = NR</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Garedia 2008</td>
<td>Retrospective cohort study</td>
<td>40</td>
<td>Mon - Thurs</td>
<td>3</td>
<td>164 [30]</td>
<td>62 [21]</td>
<td>26.8 p &lt; 0.01</td>
<td>80</td>
<td>Myalgias</td>
</tr>
<tr>
<td>Meek 2012</td>
<td>Retrospective cohort study</td>
<td>705</td>
<td>2 - 3 times a week</td>
<td>14.9</td>
<td>Daily: 4.77 [1.4]; 2 - 3 times a week: 4.77 [1.4]; once a week: 5.05 [1.6]</td>
<td>63 [10]</td>
<td>Daily: 42.2 [2.1]; 2 - 3 times a week: 32.9 p &lt; 0.001</td>
<td>89</td>
<td>Myalgias, gastrointestinal side effects, worsening of liver function tests</td>
</tr>
<tr>
<td>Kennedy 2011</td>
<td>RCT</td>
<td>17</td>
<td>Once a week</td>
<td>4</td>
<td>143 [16.1]</td>
<td>64.5 [25.3]</td>
<td>Intervention: 122; placebo: 0.4 p &lt; 0.002</td>
<td>80</td>
<td>Myalgias</td>
</tr>
</tbody>
</table>

LDL - low density lipoprotein, NR - not reported
Table 2.

<table>
<thead>
<tr>
<th>Study / publication year</th>
<th>Sample size (n)</th>
<th>Country</th>
<th>Cost comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghattas AE (2009)</td>
<td>100</td>
<td>Brazil</td>
<td>Monthly cost of 53.33 to 74.65 BRL when taken intermittently, compared to 106.85 when taken daily</td>
</tr>
<tr>
<td>Mitaaka et al. (2009)</td>
<td>35</td>
<td>United States</td>
<td>1.22 USD per 1% LDL reduction when taken on alternate days, compared to 1.71 when taken daily</td>
</tr>
<tr>
<td>Pramanik S (2012)</td>
<td>40</td>
<td>India</td>
<td>23.45 INR per 1% LDL reduction when taken on alternate days, compared to 41.43 when taken daily</td>
</tr>
<tr>
<td>Wongwitthananukit S (2006)</td>
<td>98</td>
<td>Thailand</td>
<td>38% reduction in monthly cost per 1% LDL reduction when taken on alternate days, compared to when taken daily</td>
</tr>
</tbody>
</table>

BRL = Brazilian real; USD = US dollar; INR = Indian rupee; LDL = low-density lipoprotein

Results

Search results

For the assessment of efficacy and tolerability, the initial search from databases identified 1,339 potentially relevant articles. Of these, 1,229 articles were removed for being irrelevant to the research question. Further excluded articles were duplicates, reviews, news, commentaries, and articles that evaluated combination therapy. Three randomized controlled trials (RCTs), one case report and seven cohort studies were included for full review and assessment of efficacy and tolerability (Figure 1a). The details of the included studies are provided in Table 1.

For the economic analysis, the initial search from databases identified 1,826 potentially relevant articles. Of these, 1,229 articles were removed for being irrelevant to the research question. Duplicates, reviews, news, commentaries, and articles that evaluated combination therapy were further excluded. Three RCTs and one cohort study were included for full review and assessment of efficacy and tolerability (Figure 1b). The details of the included studies are provided in Table 2.

Changes in lipid levels

All studies supported that administering statins non-daily can lower LDL levels in patients with dyslipidemia. All dosing regimens were shown to be effective. Most studies used a moderate intensity statin to administer non-daily and reported a reduction in LDL between 12.2% and 44.8%. Given that the daily administration of moderate intensity therapy lowers LDL by 30% to 50%, the reductions in LDL were clinically meaningful in most studies.14

Alternate day

Backes et al. (2008)15: A cohort study of 51 patients at two lipid specialty clinics reported a mean LDL reduction of 34.5% from baseline (p < 0.001) with every other day rosuvastatin regimen (mean dose of 5.6 ± 2.9 mg).15 The reduction in mean total cholesterol (TC) from baseline was statistically significant, but the change in HDL was not significant.

Pramanik et al. (2012)16: Forty patients were randomly assigned to receive 20 mg atorvastatin on alternate days or daily for 12 weeks with 4 weeks of washout period. At weeks 6 and 12, LDL-C and TC were significantly reduced from baseline in both groups. The difference in reduction between the groups was not statistically significant, which shows that the alternate dosing regimen is as effective as the daily dosing regimen. A slight increase in HDL levels from baseline was observed.

Three to five times a week

Goldberg et al. (2013)17: The study included 58 patients on rosuvastatin 3-4 times weekly (mean dose of 29.4 ± 14.6mg per week) at a specialty lipid. Patients had a significant reduction in LDL of 34.4 ± 21.3% (P < 0.001) at week 12 from baseline. The reduction in TC and TG levels were significant, but the change in HDL was non-significant.

Ghattas et al. (2007)18: One hundred patients were initially given atorvastatin 10mg daily after 12 weeks of dietary modifications. At week 6, patients meeting their LDL goals were switched to atorvastatin 10mg for 5 times a week. At week 12, patients still at their LDL goals were further adjusted to atorvastatin 10mg for 3 times a week. Forty-eight patients who received statin intermittently had an average of 44.6% and 31% reduction in LDL and TC levels, respectively.

Two to three times a week

Mackie et al. (2007)19: Two patients with a history of statin intolerance were switched to 2.5mg and 5mg rosuvastatin every Monday, Wednesday, and Friday. The patients tolerated the new regimen, and their LDL was significantly reduced by 20% and 38%.

Gadarla et al. (2008)20: In the study of 40 patients, the patients were treated with rosuvastatin 5mg or 10mg every Monday and Thursday to improve tolerability. The mean LDL, TC and TG levels were reduced by 26%, 19% and 14%, respectively. However, HDL level did not change significantly.
Meek et al. (2012): The study analyzed 325 patients at 9 health centers in the UK with a history of statin intolerance for a median follow-up of 14.9 months. Patients who received rosuvastatin 5 mg 2 to 3 times weekly had a mean LDL reduction of 32%, TC reduction of 26%, and TG reduction of 16% (p<0.001).

Once a week
Ruisinger et al. (2009): Fifty patients received rosuvastatin once a week (10 ± 4mg/week) due to a prior statin intolerance. There was a mean reduction of 23%, 17%, and 12% for LDL, TC and TG, respectively, and 5% increase in HDL (p <0.001). After discontinuation, the lipid levels were measured between 1 to 3 days and between 4 to 7 days since the last dose. The mean LDL level did not change significantly even after 4 to 7 days of discontinuation.

Backes et al. (2012): In the study, 51 patients were assigned to receive either rosuvastatin 80 mg once weekly or atorvastatin 10 mg daily for 8 weeks. Both regimens had significant and comparable reductions of 29% in LDL and TC of 20% from baseline. The changes in HDL and TG levels were non-significant.

Kennedy et al. (2011): The study included 17 patients who experienced myalgias from prior statin therapy. Two 8-week treatment phases consisted of rosuvastatin 5mg once weekly or matching placebo. The dose was titrated to 10mg once weekly if not at LDL goal at week 4. The mean LDL reduction from baseline was 12.2% in the intervention group compared to 0.4% in the placebo group (p=0.002). The intervention group had a greater mean reduction in TC of 10.2% compared to 3% in the placebo group. However, the mean change in HDL was non-significant. All patients were middle aged males, and the majority were Caucasian. Also, their lipid control at baseline was relatively good and close to attaining goal.
### Tolerability and adverse effects

Most studies reported high tolerability to intermittent statin therapy, ranging from 72.5 to 100%. Some of the adverse effects were myalgia, gastrointestinal complaints, and return of prior adverse effects, including fatigue, memory impairment and rash.\(^{(7)}\) In a study of 50 patients, 71% of patients who previously experienced myalgias tolerated a once weekly regimen.\(^{(14)}\) Elevation in creatine kinase and hepatic transaminase levels resolved when switched to once weekly administration in most patients. Fifty percent of the patients with prior gastrointestinal complaints and 75% with other adverse effects tolerated the new regimen.

### Economic analysis

The economic analysis of included studies showed that the intermittent regimen is cost-saving in terms of cost per 1% LDL reduction.

Matalka et al. (2002)\(^{(17)}\): Thirty-five patients were randomly assigned to receive atorvastatin either daily or on alternate days. At weeks 6 and 12, the dose was doubled for patients whose LDL goals were not met. The study reported a significant and comparable decrease in LDL in both daily and alternate dosing groups at week twelve. However, the alternate day dosing group took significantly lower average milligrams of statin per day, which resulted in 34% cost saving compared to the daily dosing group.

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**Figure 1. Study selection for (a) efficacy and tolerability assessment, and (b) cost analysis.**

<table>
<thead>
<tr>
<th>Source</th>
<th>Search Terms</th>
<th>Settings</th>
<th># of Articles Identified</th>
<th>Date Accessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane</td>
<td>MeSH descriptor: [Drug Administration Schedule] explode all trees AND MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees</td>
<td></td>
<td>175</td>
<td>September 11, 2017</td>
</tr>
<tr>
<td>Embase</td>
<td>'cholesterol'/exp AND 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp AND 'side effect'/exp AND 'myalgia'/exp</td>
<td></td>
<td>864</td>
<td>September 11, 2017</td>
</tr>
<tr>
<td>Web of Science</td>
<td>‘Intolerant’ AND ‘statin therapy’</td>
<td>Core Collection, in ‘topic’</td>
<td>168</td>
<td>September 11, 2017</td>
</tr>
</tbody>
</table>
Ghattas et al. (2007)10: In the study, patients receiving atorvastatin 10mg either five times a week or three times a week had a 30 to 50% saving per month compared to patients receiving atorvastatin 10mg daily. The patients were still able to maintain their LDL goals with the intermittent administration.

Pramani et al. (2012)8: The study included 40 patients in India. Patients received 20mg atorvastatin either on alternate days or daily. The cost of treatment was approximately 23.48 Indian rupees (INR) per 1% reduction of LDL when taken on alternate days, compared to 41.49 when taken daily.

Wongwiwatthanakanit et al. (2006)18: Eighty patients with dyslipidemia were randomized to receive rosuvastatin 10mg once daily or every other day for 8 weeks in Thailand. The monthly cost per 1% reduction of LDL was 38% lower when taken on alternate days.(7)

Discussion

Our analysis of current evidence suggests that intermittent statin administration is effective in lowering LDL levels in patients with dyslipidemia. All dosing regimens, including alternate days, 3 to 5 times a week, 2 to 3 times a week, and once a week, were shown to be effective. Non-daily administration showed other benefits of improved tolerability and lower cost when compared to daily administration. Although the reduction cardiovascular endpoints remain unclear due to short-term study duration, non-daily statin regimen may be used as an effective and safe alternative to lower LDL in patients who are not able to tolerate a daily regimen. Some of the limitations were that many of the included studies were cohort studies with small size and short-term follow-up. Non-pharmacological interventions and adherence to study medications were not assessed in many studies. For the economic analysis, the included studies were published in different countries when generics to atorvastatin and rosuvastatin were not available. Therefore, future clinical trials addressing these limitations may be necessary.

About the Authors

Dr. Cindy Park has recently completed her PharmD degree at Western University of Health Sciences, College of Pharmacy. Dr. Park has no bias to report.

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References


