1. Introduction

Hydroxymethylglutaryl Coenzyme A (HMG-CoA) Reductase inhibitors (statins) are well-established as the treatment of choice for lowering low density lipoprotein–cholesterol (LDL-C) levels and reducing cardiovascular (CV) events. Overall, these agents have a remarkable safety profile, although some patients do not tolerate them [1,2].

The most common reasons for discontinuing statin treatment include muscle related adverse events, gastrointestinal complaints, liver enzyme elevation, as well as cognitive and memory problems. Such events reportedly occur with a very low frequency in less than 5% of subjects in randomized clinical trials [3,4], but in as many as 20% in clinical practice [5]. The PRIMO observational study reported muscle complaints in 10.5% of 7924 statin treated subjects [6].

It has been proposed that statins can be administered in various non-every day regimens, which have been reported to be effective and tolerable even in cases of previous intolerance to statins [7–27].

The aims of this review were to summarize the available data on non-every day statin administration schedules, the effectiveness and tolerability of these regimens, and the indications for their use.

2. Methods

2.1. Search strategy

We searched the MEDLINE databases to identify clinical trials, case reports, and reviews on other than daily statin administration regimens, published between January 1990 and January 2010. The search terms were statins, lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, non-every day, every other day, alternate day, once a week, and twice a week. All publications regardless of methodology, design, size, or language were included.

2.2. Data extraction and synthesis

Data extracted from each article included the study design, duration, and aims, type of statin, the therapeutic regimen, patient characteristics, effectiveness (LDL-C level reduction and/or reaching target levels), adverse events, tolerability, and cost assessment.

This review is organized according to the therapeutic regimen and type of statins.

3. Results

Twenty-one articles were identified (7–27). However, the heterogeneity of the study groups, medications and doses, design and aims precluded a pooled or meta-analysis.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Objectives</th>
<th>Statin and dose</th>
<th>Study duration</th>
<th>No. of subjects (M/F)</th>
<th>No. of missing/not included subjects</th>
<th>LDL-C reduction (%)</th>
<th>Safety information</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rindone J²</td>
<td>Open, uncontrolled</td>
<td>Efficacy</td>
<td>Lovastatin 20 mg</td>
<td>6 weeks</td>
<td>21 (17/2)</td>
<td>1 – Angioedema</td>
<td>20</td>
<td>1 – Muscle cramping</td>
<td>98% compliance</td>
</tr>
<tr>
<td>Dennis VC⁶</td>
<td>Retrospective review</td>
<td>Efficacy – attained LDL-C target levels</td>
<td>Lovastatin 20 mg</td>
<td>224 ± 90 days</td>
<td>20 (20/0)</td>
<td>1 – Lost to follow up</td>
<td>20 + 10 (p&lt;0.05)</td>
<td>–</td>
<td>20% attained LDL-C goal</td>
</tr>
<tr>
<td>Copher HR⁹</td>
<td>Nonrandomized controlled</td>
<td>Efficacy</td>
<td>Simvastatin Daily dose vs. double dose alternate day</td>
<td>8 weeks</td>
<td>15 (15/0)</td>
<td>1</td>
<td>No diff.</td>
<td>No diff. in AST, ALT, CK levels</td>
<td>Cost savings up to 50%</td>
</tr>
<tr>
<td>Rindone JP¹⁰</td>
<td>Randomized, nonblinded, crossover</td>
<td>Efficacy</td>
<td>Fluvastatin 20 mg/day vs. 40 mg/alternate day</td>
<td>6 weeks</td>
<td>30 (22/1)</td>
<td>4 – Protocol violation 3 – AE</td>
<td>24% vs. 21%</td>
<td>2- Gl upset</td>
<td></td>
</tr>
<tr>
<td>Piamsomboon C¹¹</td>
<td>Open, uncontrolled</td>
<td>Safety efficacy</td>
<td>Atorvastatin 1 mg</td>
<td>8 weeks</td>
<td>60</td>
<td>1</td>
<td>–</td>
<td>30</td>
<td>Cost savings up to 50%</td>
</tr>
<tr>
<td>Matalka MS¹²</td>
<td>Double-blind, placebo controlled</td>
<td>Efficacy</td>
<td>Atorvastatin 10 mg/alternate day vs. 10 mg/day</td>
<td>12 weeks</td>
<td>18 (11/7) 10 (5/5)</td>
<td>2 – Withdraw consent 1 – Didn’t fast</td>
<td>35 vs. 38 (p=0.49)</td>
<td>–</td>
<td>43% vs.75% attained LDL-C goal</td>
</tr>
<tr>
<td>Jafari M¹³</td>
<td>Randomized, prospective, non blinded, controlled</td>
<td>Efficacy</td>
<td>Atorvastatin 10 mg/day vs. 10 mg/alternate day</td>
<td>6 weeks</td>
<td>54</td>
<td>1</td>
<td>–</td>
<td>Well tolerated. No sig. elevation of liver enz. or CKP</td>
<td>34% cost reduction</td>
</tr>
<tr>
<td>Ferrer-Garcia JE¹⁴</td>
<td>Open, controlled</td>
<td>Efficacy</td>
<td>Atorvastatin Dose/day vs. dose/alternate day</td>
<td>12 weeks</td>
<td>44 (25/19)</td>
<td>4 – AE 3 – Withdraw consent</td>
<td>39 vs. 23 (p&lt;0.05)</td>
<td>2-elevated liver enz. 2- Uncontrolled DM</td>
<td>Diabetic subjects Alternate days: 5.6% LDL-C &lt;100 mg/dl 50% cost reduction</td>
</tr>
<tr>
<td>Ghattas AE¹⁵</td>
<td>Open, controlled</td>
<td>Efficacy</td>
<td>Atorvastatin Dose/day vs. [5/ w or 3/ w]</td>
<td>6 weeks</td>
<td>52 vs. 41 (25 or 16)</td>
<td>4 – Lost to follow up 2 vs.3 – lost to follow up</td>
<td>32 vs. 42 or 46</td>
<td>No AE</td>
<td></td>
</tr>
<tr>
<td>Keleş T¹⁶</td>
<td>Prospective, randomized, controlled</td>
<td>Efficacy</td>
<td>Atorvastatin Dose/day vs. (12/28)</td>
<td>12 weeks</td>
<td>30 vs. 31 (40/21)</td>
<td>–</td>
<td>41 vs. 43 (NS)</td>
<td>–</td>
<td>CRP levels reduced 37% (p&gt;0.05)</td>
</tr>
<tr>
<td>Wongwithathananukit S¹⁷</td>
<td>Randomized, open, parallel</td>
<td>Efficacy safety</td>
<td>Rosuvastatin 10 mg/day vs. 10 mg/day</td>
<td>8 weeks</td>
<td>40 vs. 40 (17/23 vs. 15/25)</td>
<td>1 – sepsis 3 – AE</td>
<td>48 vs. 39 (p=0.153)</td>
<td>2 – Malaise and myalgia 1 – Headache No elevation of liver enz. × 3 or CPK × 10 LDL-C reduction</td>
<td>85% vs.70% attained LDL-C goal Out of 10 with prev. elevated liver enz.: 85% cost reduction 1% LDL-C reduction</td>
</tr>
<tr>
<td>Backes JM¹⁸</td>
<td>Retrospective analysis</td>
<td>Efficacy Tolerability</td>
<td>Rosuvastatin 5.6 mg/alternate day</td>
<td>4 ± 2.9 months</td>
<td>51 (23/28) 14 – AE</td>
<td>34</td>
<td>10 – Myalgia 1 – GI comp. 1 – Fatigue 1 – Memory impairment 1 – Rash</td>
<td>No AE, specifically myalgias Previous atorvastatin intolerance</td>
<td></td>
</tr>
<tr>
<td>Mackie BD¹⁹</td>
<td>Case report</td>
<td>Case report</td>
<td>Rosuvastatin 2.5, 5 mg 3/w</td>
<td>6 weeks</td>
<td>2 (1/2)</td>
<td>–</td>
<td>38, 20</td>
<td>–</td>
<td>Previous atorvastatin intolerance</td>
</tr>
<tr>
<td>Dulay D²⁰</td>
<td>Cross over</td>
<td>Efficacy</td>
<td>Rosuvastatin 10 mg/day vs. 20 mg/alternate day</td>
<td>6 weeks</td>
<td>45 (24/21)</td>
<td>6</td>
<td>48.5 vs.40.9 (p=0.012)</td>
<td>No major complications 1 – Myalgia, resolved GI upset - most common</td>
<td></td>
</tr>
<tr>
<td>Juszczysz MA²¹</td>
<td>Open</td>
<td>Report of clinical experience</td>
<td>Atorvastatin 18.8 mg 3/w rosuvastatin 9.7 mg 1/w</td>
<td>3.3 ± 3.0 months</td>
<td>9, 16 (17/8)</td>
<td>–</td>
<td>28, 43</td>
<td>–</td>
<td>12/25 Resolution of previous myalgia</td>
</tr>
</tbody>
</table>
3.1. Alternate day regimens

Fifteen studies reporting an alternate day statin treatment regimen were found [7–21]. Their design and details are provided in Table 1.

Most of the studies were of short duration, lasting 6–18 weeks. Only one study (with atorvastatin) was double-blinded and placebo-controlled [12]. The study groups were small, usually several dozen subjects, and were composed mainly of individuals treated for “primary prevention” [7–13,16–21].

All studies reported a significant reduction in LDL-C levels. No controlled study found clinically significant differences in LDL-C level reduction between daily and alternate day statin administration [9,10,12–17,19,20].

The efficacy of the alternate day regimens was also shown by the rate of reaching the LDL-C target levels. An LDL-C level < 100 mg/dl was achieved by 57.6% of diabetic patients treated with a mean dose of 5.6 mg atorvastatin [14], while 70% and 50% achieved the LDL-C target level with rosuvastatin at a mean dose of 10 mg [13,18]. Only 20% of the subjects attained their LDL-C goal level with 20 mg lovastatin on alternate days [8].

One study evaluated the effect on C-Reactive Protein (CRP) levels. The authors reported no difference in the reduction of either LDL-C or CRP levels when atorvastatin was administered at a dose of 20 mg/day or on alternate days [16].

The alternate day statin administration regimens using rosuvastatin and atorvastatin were reported to be well tolerated, even among subjects with previous statin intolerance [18–20]. Cost analysis revealed meaningful savings of 30–50% with alternate day compared with daily regimens [14,15,17].

3.2. Twice weekly regimens

The change of simvastatin from 10–20 mg/day to 40–80 mg twice a week was not effective in terms of both LDL-C level reduction and reaching LDL-C target levels [22]. Nevertheless, rosuvastatin 5 mg or 10 mg twice a week significantly decreased LDL-C levels by 26% [23] (Table 2).

3.3. Once a week regimens

The regimen of 5–20 mg rosuvastatin once a week was reported in eight patients with intolerance to daily statin regimen. All patients tolerated the weekly regimen well and achieved a meaningful reduction in LDL-C levels [24] (Table 2).

3.4. Non-every day statins combined with other lipid-lowering agent regimens

Two studies reported successful use of various statin regimens combined with other lipid-lowering agents in patients with intolerance to daily statin regimens [25,26]. Two other studies reported no significant differences when another medication was added [23,27] (Table 2).

4. Discussion

The literature review on less frequent statin treatment regimens revealed that the available data are lacking. The studies were characterized by small sample sizes, short follow up durations, inclusion of more males than females, more “primary” than “secondary” prevention cases, varying endpoints, and lack of randomization or control groups in many.

The heterogeneity of the study groups, medications, and doses, as well as their design and aims, precluded the performance of a meta-analysis or pooled analysis. However, certain conclusions can be drawn concerning these uncommon methods of statin administration. First, they should be applied to patients who cannot tolerate statins or who have had adverse events that prevent their administration on the common daily dose basis. Second, the most reported and most successful regimen is alternate day administration. Although most statins have favorable effects, it is advisable to use mainly atorvastatin and rosuvastatin because of their pharmacological profile. Both are very potent statins and have a prolonged effect on reducing LDL-C levels. The half-life of atorvastatin is about 14 h, while its HMG-CoA Reductase inhibition reaches 20–30 h [28]. Rosuvastatin’s half-life is 19 h and in contrast with other statins (e.g. lovastatin, simvastatin, or atorvastatin), it is primarily cleared by the feces and is minimally metabolized (~10%) by the CYP2C9 isoenzyme. Thus, it is less likely to be involved in common drug interactions [29–31]. However, the effect of these two agents on LDL-C level reduction or their tolerance in the non-every day regimens has not yet been compared.

Theoretically, the option of combining a less frequent statin regimen with other lipid lowering agents is promising. These combinations were reported for once or twice a week administration of atorvastatin and rosuvastatin in combination with ezetimibe, fibrates, resins, or Chinese red rice. However, the efficacy in lowering LDL-C levels was unremarkable and the clinical implications were not studied [23,25–27].

Patients cooperated with the less frequent regimens. The mean compliance with one of the alternate day regimens was 98% [7], while in another study, 17 of 31 subjects reported equal convenience or preferred a twice weekly to a daily treatment regimen [22]. The less frequent statin regimens were used successfully in many such patients who could not tolerate the daily schedules [18,21,23–27]. As many reports indicate that higher statin doses are associated with increasing muscle symptoms, it is likely that reducing the dose will contribute to their tolerability. It is also possible that intermittent dosing allows some muscle recovery from the myopathic effect of statins and therefore increases tolerance. There might also be a psychological component to the effectiveness of these regimens [23,25].

The less frequent schedules were found to have a favorable cost benefit effect due to reduced expenses [32]. However, this important issue might be less relevant today, as many generic versions of statins are becoming available.

The studies reviewed were designed to evaluate the LDL-C level lowering efficacy and the tolerability of the non-every day statin regimens. Although these aims were achieved in most studies, the effects on CV events and on the atherosclerotic process were not evaluated. Thus, the primary use of these regimens should be in patients who cannot tolerate daily statin therapy.

In our opinion, less than daily statin treatment regimens are advisable for patients who are intolerant to statin therapy. The definition of statin intolerance should include patients who developed statin-
Table 2
Studies with other Non-every day statin regimens.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Objectives</th>
<th>Statin and dose</th>
<th>Study duration</th>
<th>No. of subjects (M/F)</th>
<th>No. of missing/not included subjects</th>
<th>LDL-C reduction (%)</th>
<th>Safety information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangin</td>
<td>Open, non-randomized</td>
<td>Efficacy</td>
<td>Simvastatin</td>
<td>12 weeks</td>
<td>41 (30/1)</td>
<td>3 — protocol violation</td>
<td>+14%</td>
<td>1 — MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety</td>
<td>10/20 mg/day vs. 40/80 mg/twice a week</td>
<td></td>
<td></td>
<td>3 — Withdraw consent E</td>
<td></td>
<td>1 — Muscle soreness</td>
</tr>
<tr>
<td>Gadarla M</td>
<td>Open, retrospective</td>
<td>Efficacy</td>
<td>Rosuvastatin</td>
<td>3 months</td>
<td>14</td>
<td>26%</td>
<td></td>
<td>8 — Muscle-related symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety</td>
<td>5 mg or 10 mg/twice a week Rosuvastatin</td>
<td>3 months</td>
<td>26 (18/22)</td>
<td>2 — A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cost Satisfaction</td>
<td></td>
<td></td>
<td></td>
<td>1 — Elevated LDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raisinger</td>
<td>Open, retrospective</td>
<td>Efficacy</td>
<td>Rosuvastatin</td>
<td>2.75–8.75 months</td>
<td>10 (2/6)</td>
<td>6–62%</td>
<td>2 — Same as with daily dosing 10-myalgia</td>
<td></td>
</tr>
<tr>
<td>Athyros VG</td>
<td>Open, prospective</td>
<td>Efficacy</td>
<td>Atorvastatin 10 mg/twice a week plus ezetimibe</td>
<td>4 ± 2 months</td>
<td>50</td>
<td>23%</td>
<td>1 — No change in high CPK 1 — CI comp 1 — Other</td>
<td></td>
</tr>
<tr>
<td>Reddy KJ</td>
<td>Open</td>
<td>Efficacy</td>
<td>Rosuvastatin 5–40 mg/twice a week or atorvastatin 20–40 mg twice a week plus ezetimibe or resin</td>
<td>4.5 months</td>
<td>23 (9/14)</td>
<td>37%</td>
<td>3 — Fatigue and myalgia</td>
<td></td>
</tr>
</tbody>
</table>

AE — adverse events.
associated adverse effects. These might be either recognized by the physician or identified by the patient, who finds his quality of life so diminished by these adverse effects that he discontinues treatment [33]. The evaluation of such patients should be systematic and include, ruling out possible causes for statin intolerance, “statin holiday” and re-challenge, and as different risk profiles are associated with various statins and dosages, dose reduction or switching to better tolerated statins, such as pravastatin or fluvastatin, should be considered [4,5]. However, low potency statins might also be poorly tolerated, as high doses might be required. The use of other lipid lowering agents is less recommended, because they have lower potency (resins, ezetimibe, fibrate, niacin), have high rates of intolerance (resins, niacin), or have not yet been proven to affect CV outcomes (fibrates, ezetimibe) [34]. Based on the above data, the non-every day statin treatment regimens should be considered one of the preferred alternatives in patients with statin intolerance. It is advisable to prescribe the more potent statins (atorvastatin or rosuvastatin) in alternate day regimens. However, further studies are needed to clarify the effect of these less frequent regimens on CV events.

Learning points
- Data on non-every day statin regimens are lacking.
- The most reported and successful regimen is alternate day administration, using mainly atorvastatin and rosuvastatin.
- Non-every day regimens should be used primarily for patients who cannot tolerate daily statin therapy.
- Further studies are needed to clarify the effect of less frequent regimens on cardiovascular events.

Conflict of interest
There is no conflict of interest and both authors have read the manuscript.

References
[23] Cadarla M, Kearns AK, Thompson PD. Efficacy of rosuvastatin (5 mg and 10 mg) twice a week in patients intolerant to daily statins. Am J Cardiol 2008;101:1747–8.