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Migraine Prophylaxis: A Review of Current and Future Therapies

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Migraine is defined by the World Health Organization (WHO) as a complex neurologic disorder that commonly manifests itself in moderate to severe pain that impacts women more than men by 2:1.[1] According to the Migraine Research Foundation, 38 million Americans are affected by migraines and is the 6th most disabling illness in the world.[2] A migraine usually, but not always happens in 4 phases: the premonitory phase, the aura phase, the headache phase and the postdrome phase.

There is still debate in regards to the pathophysiological mechanisms behind what contributes to migraines. It was originally presumed that vasodilation of the cranial and cerebral vessels was what lead to pain during migraine attacks.[3] However, this notion has been debunked in the mid 1990's in studies such as Woods and colleagues who found hypoperfusion of the vessels during pain and Kruse who found no changes in cerebral artery diameter during sildenafil-induced migraine.[4,5] One of the more prominent theories recently is the idea of cortical spreading depression as the culprit for migraines. However, this is more associated with the aura phase of the migraines rather than the headache phase. Mutations of genes, specifically CACNA1A, ATP1A1, and SCN1A can increase risk of cortical spreading depression as well as effect neuronal firing frequency. Along with these mutations, inflammatory genes such TNFRSF1B, IL1B, IL9, CCR2 and PTGS2 can also increase the risk of migraine attacks. It has also been theorized that certain mutations in neurotransmitter genes, such as GRIA1 and 3, CPQ, GABRB3 and DRD2 have been associated with migraines.[6]

Migraines can be classified into either episodic or chronic based on the number of migraine days a patient suffers per month. Migraines are classified as chronic if a patient suffers at least 15 headache days per month, 8 of which meet the criteria for migraine as defined by the International Classification of Headache Disorders.[7] It is this population that would be the primary candidate for migraine prophylaxis. Though there has been much research and investment into acute treatment of migraines, preventative measures are still an area that needs to be addressed. The purpose of this article is to look at current migraine prophylactic treatments, both FDA approved and off-label, their respective mechanisms of action, and whether or not they are efficacious in reducing and preventing migraines.

Current Therapies

There are several medications that have been approved for the management of migraine prophylaxis as well as many that are used "off-label" These medications are summarized in **Table 1**. Their strength of evidence for each treatment based on American Academy of Neurology's (AAN) recommendations.[8] The AAN reviewed all English randomized control trials (RCTs) between 1997 and 2007. The trials were then categorized as either Class I or II based on pre-established criteria and evaluated by two independent panelists, with Class I being the highest quality randomized controlled.[8] Medications were categorized into Class A (≥ 2 Class I RCTs), Class B (1 Class I RCT or 2 Class II RCTs), Class C (1 Class II RCT) and Class U (inadequate evidence).

Beta-blockers

ß-blockers work primarily through vasodilation of the blood vessels through adrenergic receptors and inhibition of the sympathetic response. The exact mechanism by which it prevents migraines remains unclear, though their inhibition of catecholamine-induced lipolysis pathways has been a suggested cause for migraine prevention.[9]

One of the earliest studies to investigate propranolol's efficacy was done by Rosen and colleagues.[10] In their study, they looked at patient-recorded migraine severity between propranolol 325 mg and placebo (controls not defined) for at least 1 year.[15] The authors found a statistically significant reduction in migraine symptoms with a reported 84% improvement in the propranolol group compared to 32% improvement in controls ($p<0.01$).[10] Kuritzky and Hering completed a 16 week cross-over study that compared 160 mg long-acting propranolol with placebo.[11] In their cross-over study, they found a significant reduction in the number of migraine attacks (3.23 days in the propranolol group vs. 5.56 days in the placebo group; $p=0.014$) and patient's recorded severity (mean 15.66 propranolol vs mean 25.66 placebo; $p=0.003$). One limitation of their report, however, was they did not report blinding or the exact statistical testing in their study. More recently, Rao and colleagues conducted a double blind, placebo controlled study. In the study, patients were given either placebo, propranolol 40 mg twice daily, cyproheptadine 2 mg twice daily, or a combination of

Table 1 | Summary of drugs for migraine prophylaxis.

Drug	AAN Classification[a]	Medication Class	Recommended Dose	Duration
FDA Approved				
Onabotulinumtoxin A	None	Intramuscular toxin	155 units administered in 5 units injections across 31 sites	Every 3 months
Propranolol	A	ß-blocker	IR: 80mg PO QD in divided doses; may increase to 160-240mg daily ER: 80mg PO QD divided; may be increased to 160-240mg daily	Discontinue if no improvement after 4-6 weeks
Timolol	A	ß-blocker	Initially 10mg QD; may be titrated up to a maximum of 30mg QD	Discontinue if no improvement after 8 weeks
Topiramate	A	Antiepileptic	Initially 25mg QHS Week 1, 25mg BID week 2, 25mg QAM and 50mg QHS week 3, and 50mg BID week 4	Indefinite
Valproic Acid	A	Antiepileptic	Initially 250mg PO BID, then titrate up to 500mg PO BID	Indefinite
Off-label				
Fluoxetine	U	SSRI	20-40mg PO QD	Indefinite
Venlafaxine	B	SNRI	37.5 mg PO QD for 3 days, followed by 75mg PO QD for the next 3 days prior to increasing to 150mg PO QD	Indefinite
Amitriptyline	B	TCA	Initially 25mg PO QD, then titrate to well tolerated and efficacious	Indefinite
Lisinopril	C	ACE-I	Initially 10mg PO QD for 1 week, then 20mg PO QD	Indefinite
Candesartan	C	ARB	16 mg PO QD	Indefinite
Nifedipine	U	CCB	30-180mg PO QD	Indefinite
Atenolol	B	ß-blocker	100mg PO QD	Indefinite
Metoprolol	A	ß-blocker	Tartrate: Initially 25mg PO BID, then titrate to response Succinate: 50mg PO QD, then titrate to response	Indefinite
Nadolol	B	ß-blocker	80mg PO QD; up to 240mg has been studied	Indefinite
Nebivolol	C	ß-blocker	5mg PO QD	Indefinite
Naproxen	None	NSAID	250mg PO BID or TID; not to exceed 1000mg QD	Indefinite
Fenoprofen	None	NSAID	200-300mg PO TID	Indefinite

[a]Class A (≥ 2 Class I RCTs), Class B (1 Class I RCT or 2 Class II RCTs), Class C (1 Class II RCT) and Class U (inadequate evidence).
ACE-I = angiotensin converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **BID** = twice daily; **CCB** = calcium channel blocker; **PO** = oral; **QAM** = morning; **QD** = daily; **QHS** = hours of sleep; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **TID** = three times daily

the two for three months and were compared through one-way ANOVA. The authors found a reportedly statistically significant reduction in severity and frequency of migraines in all three treatment groups compared to placebo.[12] However, A recent comparative effectiveness meta-analysis looked at the use of several ß-blockers for preventing migraines. This analysis showed all ß-blockers were superior in preventing migraines when compared to placebo. Specifically, this analysis found that propranolol reduced the number of headaches/month (HA/month) by -1.1 (95% CI -1.5 to -0.74) at 4 weeks and -1 (RR -2.1 to -0.39) at 8 weeks. They also found that metoprolol, atenolol, and timolol reduced incidences of migraines by -0.94 (95% CI -1.4 to -0.46) HA/Month. Overall, all ß-blocker studies showed improvement only in episodic migraines and no ß-blocker was found to help with chronic migraine.[13]

Antihypertensive Agents

In addition to ß-blockers, other antihypertensive medications have been used off-label for the treatment of migraine prophylaxis. Lisinopril, an angiotensin converting enzyme inhibitor (ACE-

I), candesartan, an angiotensin receptor blocker (ARB), and nifedipine, a calcium channel blocker (CCB), are also possible agents used in the prevention of migraine. Both ACE-Is and ARBs primarily inhibit the renin-angiotensin systems; whereas, CCBs inhibit the influx of extracellular calcium into the cardiac and smooth muscle cells. However, like ß-blockers, the exact mechanism of action that these drugs have on the prevention of migraines is still undetermined. The AAN supports the use of lisinopril and candesartan as being potentially effective as preventative therapies, but does not support nor refute the use of nifedipine in headache prevention.[8]

In a study conducted by Schrader and colleagues, lisinopril 10 mg was found at 12 weeks to lead to a significant reduction in headaches by 20% (95% CI 5% to 36%), migraines by 21% (95% CI 9% to 34%), and hours with headaches by 20% (95% CI 5% to 35%) when compared to placebo.[14] In a triple-blind, placebo controlled crossover study, researchers compared candesartan 16 mg to propranolol 160 mg.[15] Both candesartan and propranolol were found to be superior to placebo by reducing migraine days per month to 2.95 and 2.91, respectively, compared to 3.53 days with placebo (p=0.02 for both treatment groups). Candesartan and propranolol also had response rates of 43% and 40%, respectively, compared to a response rate of 23% with placebo (p=0.025 for candesartan and p<0.05 for propranolol).

In regards to the use of CCBs in preventing migraines, the data still remains sparse and inconclusive. A 1989 12-week study with 24 patients, nifedipine did not significantly reduce headache days (average 2.1 ± 0.2 days) compared to placebo (average 2.3 ± 0.2 days) at any of the monthly checkpoints (p=0.31 for month 1, p=0.43 for month 2, p=0.56 for month 3)[16] The author also stated that due to it's limited sample size (n=24), the study would have not allowed for a 50% or large decrease in headache frequency at p< 0.05 confidence level. However, in a 1995 double blind crossover study, there was a significant difference in Headache Index response (attacks/month x severity x duration) between placebo (14% of group showed improvement) and nifedipine (71% of group showed improvement).[17]

Antidepressants

There are two tricyclic antidepressants (TCAs), one selective norepinephrine reuptake inhibitor (SNRI) and one selective serotonin reuptake inhibitor (SSRI) that have been used for migraine prevention. Depending on the specific agent, antidepressants, in general, inhibit the reuptake of neurotransmitters, namely serotonin and norephinephrine, leading to elevated concentrations of these neurotransmitters within the synapse. Though the exact mechanism of reducing the incidence of migraines has not been thoroughly studied, the most popular theory is their increased serotonergic activity in the trigeminal system. The AAN guidelines define amitriptyline, nortriptyline, venlafaxine as being probably effective while stating there was inadequate data to support fluoxetine.[8]

In a 26-week double-blind, double-dummy, parallel-group non-inferiority study, amitriptyline 25 mg daily showed no significant difference when compared to topiramate 25 mg daily (-2.6 vs -2.7 least square mean difference in migraine episode reduction {CI -0.6 to 0.7} respectively), in the reduction of episodic migraine days.[18] However, in Jackson and colleagues' network meta-analysis, amitriptyline showed superiority to topiramate (p=0.005) in reducing headache days per month.[13] The authors pooled data for drugs studied in randomized controlled trials (RCA's) that were at least 4 weeks in duration. A 6.5-month retrospective cohort study also looked at three different starting dose groups of amitriptyline in preventing migraines: very low (≤10 mg daily), low (11-25 mg daily) and traditional (≥25 mg daily).[19] Though there was a combined patient-reported improvement in 74% of patients, the study did not have any analysis beyond descriptive statistics and acked blinding; patients also did not use a headache journal to document headache severity. In a study done by Ozyalcin and colleagues, venlafaxine 75 mg and 150 mg showed superiority to placebo in patient satisfaction (p=0.001), daily activities (p<0.001) and reduction in analgesic consumption (p=0.001).[20] In a network meta-analysis that analyzed the cumulative reduction of headache days from multiple studies, only the venlafaxine 150 mg group showed a significant reduction in comparison to the others, while fluoxetine was found to have no benefit over placebo in either reducing headaches by 50% or in the use for chronic headaches.[13]

Table 2 | Meta-analysis results of valproate and topiramate.[13]

Time (weeks)	Heterogeneity (I^2)	Average HA/month reduction	95% CI
Valproate			
4	86.70%	-2.57	-4.12 to -1.03
8	53.90%	-1.48	-2.20 to -0.76
12	86.70%	-1.5	-2.1 to -0.8
Topiramate			
4	75.10%	-1.21	-1.92 to -0.51
8	45.70%	-1.47	-2.07 to -0.87
12	0.00%	-1.49	-1.93 to -1.06
16	47.90%	-1.08	-1.72 to -0.44
20	0.00%	-1.37	-1.82 to -0.91

HA = headache

Anticonvulsants

Both topiramate and valproate are FDA approved for migraine prevention and AAN classifies both as Class I recommendations. Topiramate inhibits cortical spreading through reduction of abnormal discharges and can block voltage-gates sodium channels and valproate theoretically increases the amount of GABA present in the brain. Both of these may help decrease the cortical spreading depression that leads to migraines.

Using a primary endpoint of monthly migraine reduction, Silberstein and colleagues randomized patients to placebo, topiramate 50 mg, 100 mg and 200 mg groups.[21] Compared to the reduction seen with placebo (26%) over 26 weeks, topiramate 50 mg, 100 mg and 200 mg showed a reduction in frequency by 35.9% (p=0.04), 54% (p<0.001) and 52.3% (p<0.001), respectively. In a similar 26-week study, Brades and colleagues found similar efficacy in reduction of migraine days with the 100 mg (p=0.003) and 200 mg doses (p<0.001), but not for the 50 mg dose.[22] In a 1992 double-blind study, sodium valproate 400 mg daily was found to have 8 fewers migraine attacks when compared with placebo (p<0.001), and migraines were also reported to be less severe in the valproate group (p<0.005).[23]

A recent meta-analysis for both valproate and topiramate

Table 3 | Summary of select results from PREEMPT Phase 3 Trials.[30]

Outcomes	Onabotulinum Toxin	Placebo	Mean intergroup difference (95% CI)	P-value
Headache days	-8.4	-6.6	-1.8 (-2.52,-1.13)	<0.001
Migraine days	-8.2	-6.2	-2.0 (-2.67, -1.27)	<0.001
Moderate/severe headache days	-7.7	5.8	-1.9 (-2.62, -1.26)	<0.001
Total headache hours	-119.7	-80.5	-39.2 (-48.4, -21.04)	<0.001
HIT-6 scores	67.60%	78.20%	-10.6% (-15.2%, -5.9%)	<0.001
Headache episodes	-5.2	-4.9	-0.3 (-1.17, -0.17)	0.009
Migraine episodes	-4.9	-4.5	-0.4 (-1.20, -0.23)	0.004
Acute headache medications	-10.1	-9.4	-0.7 (-2.68, 0.69)	0.247
Triptan intake	-3.2	-2.1	-1.1 (-1.74, -0.61)	<0.001

HIT-6 = headache impact test

have shown to reduce the number of migraine days (**Table 2** provides a summary of the studies). The author took the weighted mean difference (WMD) of the reduction in headaches per month from each study groups and measured the heterogeneity among the individual studies (I^2). Due to the high dissimilarities among the valproate groups, a standardized mean difference (smd) of headaches per month was used. The doses of the studies used for topiramate were 50-200 mg and valproate doses ranged from 500-1500 mg.[13] Both medications showed statistical superiority to placebo at 4, 8 and 12 weeks, while topiramate showed efficacy at 16 and 20 weeks as well. Both drugs were found to reduce headaches by 50%, though only topiramate had a suggested benefit in reduction for chronic migraine.[13]

NSAIDs

Non-steroidal anti-inflammatory inhibitors are one of the most common classes of drugs used in abortive treatment of migraines. These drugs act through inhibition of both COX-1 and COX-2, leading to a reduction in prostaglandin and thromboxane, thereby producing an analgesic and anti-inflammatory effect. Two NSAIDs, naproxen and fenoprofen, have been previously studied for their efficacy in migraine prophylaxis.[9,13] The only evidence that has previously been published for fenoprofen's efficacy was a single double-blind study performed to establish statistical significant superiority to placebo. The study investigated doses of fenoprofen at 200 mg three times daily and 600 mg three times daily for 12 weeks.[24] They did find a 50% improvement in the headache index (HA/month x severity x duration) for the 200mg dose ($p<0.05$) and the 600mg dose ($p<0.005$). Naproxen has the highest level of evidence among NSAIDs with multiple placebo-controlled trials supporting significant reduction in migraine episodes. In the initial AAN guidelines, naproxen was given a Grade B for migraine prevention, indicating that there were a few randomized trials to support its use, but not enough for to conclude a consistent patterns of findings.[25] The exact trials that evaluated the efficacy of naproxen were not included in the initial guidelines, and current guidelines have no additional evidence to support naproxen or any NSAID for migraine prophylaxis.[8]

Botulinum Toxin

Botulinum toxin was approved for use in treatment of chronic migraines on October 10, 2015.[26] It is also the first FDA approved medication for chronic migraine prevention. Unlike other agents, botulinum toxin is administered through multiple injections to the head and neck every 12 weeks. Botulinum toxin is an intramuscular toxin from the fermented *Clostridium botulinum* which primarily works in the nerve terminals by inhibition of acetylcholine release.[9] This in turn leads to a relaxing effect through muscle paralysis. One proposal is that the inhibition of the trigeminal nerve pathway leads to the relief of migraines. This was shown when onabotulinum toxin reduced trigeminal and cervical nociceptive activity after patients received an injection of capsaicin.[27] It has also been proposed that inhibition of the nociceptive neurons' substance P, glutatamate, and calcitonin-gene related peptide contribute to the analgesic effect for migraines.[28]

Botulinum has been shown to have a high level of evidence in its support of migraine prevention. The major studies to initially show this were the PREEMPT studies.[29] The phase 3 clinical trials had an initial 24-week randomized, double-blind phase then a 32-week open-label phase with the patients receiving injections every 12 weeks and visiting every 4. The final sample population was 1384 patients, which found significant decreases in migraine days ($p<0.001$), and headache severity ($p<0.001$) as seen in **Table 3**. There were also clinically significant differences with Headache Impact Test (HIT-6) scores and Quality of Life measures reported.

In regards to additional evidence to support efficacy, Guerzoni and colleagues followed patient past one year looking at headache index and analgesic use for 18 months.[30] They found a significant reduction in headache index (34% reduction from baseline; $p<0.001$) and analgesic consumption (67% reduction from baseline; $p<0.001$), as well as significant differences in HIT-6 ($p<0.01$), visual analog scale ($p<0.01$) and quality-of-life secondary endpoints ($p<0.05$) at 18 months. However, it was not stated in the study whether the results were clinically significant or not, and the population was older than the cohort included in the PREEMPT study. Negro and colleagues did a 2-year comparison of giving 195 units compared to 155 units of onabotulinumtoxin A in both chronic migraine and medication overuse headache. Over a 24-month period, the authors found no significant differences in the adverse events reported between the groups, but a significant difference in headache index , migraine days, HIT-6, and medication use. A prospective study conducted by Castrillo and colleagues investigated the efficacy of onabotulinum toxin A utilizing the PREEMPT protocol over a 16-month duration.[31] Using a two-way ANOVA, the authors found a significant reduc-

tion in headache days (12.87-day reduction from baseline; p<0.001) and headache severity (2.6 severe episode reduction from baseline; p<0.001) among patients with chronic migraines.

Future Targets

Calcitonin-gene related peptide (CGRP)

Calcitonin-gene related peptide is a pro-inflammatory neuropeptide released from both the trigeminal sensory afferents and spinal trigeminal nucleus. It is currently the best marker for migraine attacks as seen with significant elevations.[32] It is also shown as a potential migraine preventative target, as there are several monoclonal antibodies that have shown superiority in clinical trials and established at least non-inferiority to onabotulinumtoxinA in chronic migraine prophylaxis. Currently, erenumab, is showing potentially promising results in the STRIVE, ARISE and phase 2 studies for chronic migraines.[33]

Conclusion

There are multiple treatments for migraine prophylaxis. Propranolol, topiramate and valproate has shown the most evidence to support its efficacy; while NSAIDS, antidepressants and antihypertensives requires more evidence to support its use. These agents were shown to be efficacious for the prevention of episodic migraines, but currently have limited efficacy for chronic migraine prophylaxis. At this time, onabotulinumtoxin A is the only FDA approved drug for migraine prophylaxis in patients with chronic migraines, with CGRP antagonist showing potential as future therapy. As our understanding of the precise pathophysiological mechanisms behind migraines continues to grow, future studies may help shed light on other potential targets for the prevention of migraines.

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Evolocumab (Repatha®): A New Agent for Treatment of Hyperlipidemia

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Controlling cholesterol with statins, the current standard of care, has proven benefits with regards to patient morbidity and mortality. What is less clear is whether additional agents used in conjunction with a statin provide these same benefits. There is limited evidence with other classes of lipid lowering medications outside those of the statin class of medications. One clinical trial that supports the use of adjunctive lipid lowering therapy in addition to a statin is the IMPROVE-IT trial, which showed health benefit with additional lowering of low density lipoprotein cholesterol (LDL-C) beyond that of a statin alone.[1] The IMPROVE-IT trial provided a basis for the idea that a medication, such as evolocumab, being used adjunctively with a statin to lower LDL-C may provide a clinically significant benefit.

This new medication class, which includes Repatha® (evolocumab) and Praluent® (alirocumab), are injectable medications with the potential to decrease LDL-C by greater than 50% on top of the lipid lowering benefit of statin medications.[2,3] A particular population group that may benefit from these medications are individuals with either heterozygous or homozygous familial hypercholesterolemia. This is a genetic mutation that leads individuals to having relatively high levels of LDL-C which can not typically be managed to reasonable levels with statin medications. The purpose of this article is to investigate the current and future research surrounding a novel class of medications, PCSK9 inhibitors and the potential impact these medications could have on our healthcare system.

Clinical Pharmacology

Mechanism of Action

Evolocumab is a human monoclonal IgG2 antibody directed against human PCSK9 proteins. PCSK9 is a protein that naturally circulates in human blood and binds to LDL receptors in the liver. This LDL receptor is responsible for removal of LDL from the blood. Once this binding occurs, the LDL receptor is endocytosed and the receptor is destroyed. Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDL receptor. As a result of this, the LDL receptor does not undergo intracellular degradation as normal. The receptor is therefore able to recycle back to the liver cell surface and continue extracting LDL-C from the blood. Due to the increase in overall LDL receptors available when evolocumab is used, more LDL-C is extracted, leading to a lower overall level of LDL-C.[4]

Pharmacokinetics

Evolucumab is administered as a subcutaneous injection. At low concentrations, evolocumab is eliminated mostly through saturable binding to PCSK9. At high concentrations, evolocumab is eliminated mostly via a non-saturable proteolytic pathway. The half-life is approximately 11 to 17 days.[4]

The median time to peak serum evolocumab concentration following administration of either the single doses of 140 mg or 420 mg is 3 to 4 days. Maximum effect on free circulating PCSK9 proteins occur within 4 hours following administration and returns to baseline once evolocumab concentrations are undetectable. Evolocumab exhibits non-linear pharmacokinetics. Trough levels after a single injection may be expected to accumulate to a level 2 to 3 times the initial trough after reaching steady state using the bi-monthly or monthly injections. Steady state is reached within 3 months of administration. The absolute bioavailability after subcutaneous administration is approximately 72 percent.[4] **Table 1** provides a summary of the pharmacokinetics of evolocumab.

Table 1 | Pharmacokinetics of evolocumab.[4]

Property	Evolocumab
T_{max}	3-4 days
$T_{1/2}$	11-17 days
F	72%
V_d	3.3 L
Elimination	Via saturable binding to PCSK9 at low concentrations or non-saturable proteolytic pathway at high concentrations
Time to steady state	12 weeks

F = bioavailability; **Tmax** = time to reach maximum concentration; **$T_{1/2}$** = half-life; **V_d** = volume of distribution

Table 2 | Summary of Osler 1 & 2 trials.[2]

	Osler 1	Osler 2
Design type	Open-label, randomized, placebo-controlled study	
Number of subjects	1,324	3,141
Trial type	Phase 2	Phase 3
Dose of evolucumab	420 mg SQ once monthly	140 mg SQ twice monthly or 420 mg SQ monthly
Duration	56 weeks	48 weeks
Primary endpoint	Incidence of adverse events	
Secondary endpoint	% change in LDL-C at week 12	
Premature DC of study drug	7.2% of patients	
Baseline LDL-C (mean)	133 mg/dL	114 mg/dL
Mean % reduction in LDL-C	55%	64%
Mean absolute reduction in LDL-C	74 mg/dL	73 mg/dL

DC = discontinuation; **LDL-C** = low density lipoprotein cholesterol; **SQ** = subcutaneous

Drug Interactions

When coadministered with a high-intensity statin, there was an observed decrease in the AUC and Cmax of evolocumab by approximately 20%. This does not appear to be clinically significant and therefore does not alter the recommended dose in any way.[4] It is worth noting however, that due to the limited studies conducted with this medication, it is possible that significant drug interactions exist but have not yet been identified.

Clinical Trials

OSLER-1 and OSLER-2

Elevated LDL-C is associated with an increase in major cardiovascular events.[5] As a result of this, LDL-C reduction has been a focal point of clinical guidelines as a method of reducing cardiovascular morbidity and mortality. In order to evaluate the long-term safety, side-effect profile, and LDL-C reduction when using evolocumab, investigators conducted the OSLER-1 and OSLER-2 trials. In order to qualify for one of these two studies, the participants were required to complete one of twelve parent studies that were designed to evaluate the safety of the drug before it was studied on a larger scale. After completing one of these parent studies, each patient had the option of joining one of two long-term extension trials which became known as the OSLER 1 (phase 2) and OSLER 2 (phase 3) trials which were both open-label studies evaluating safety and efficacy of LDL-C reduction with the use of evolocumab. Patients were able to enroll in the extension study if they completed one of the aforementioned parent trials without an adverse event causing discontinuation of the study drug, did not have an unstable medical condition, and were not expected to need unblinded lipid measurements or adjustments of background lipid-regulating therapy during the first 12 weeks of the parent trial.[2,3] A brief summary of the OSLER 1 and 2 trials are provided in Table 2.

In the OSLER 1 and OSLER 2 trials, patients were randomly assigned to receive either evolocumab plus standard therapy of a statin based approach to cholesterol management or standard therapy alone in a 2:1 ratio.[2,3] Participants in the OSLER 1 study were administered a dose of 420 mg once a month. OSLER 2 allowed the participants to choose either 140 mg twice monthly or 420 mg once monthly. Both doses have demonstrated similar efficacy in previous studies.[2,3] Both regimens have been shown to reduce LDL-C levels by approximately 60% in previous research.[2,3] These trials were unblinded; therefore the patients, investigators, and primary care providers were aware of the randomized treatment assignments.

Between the OSLER 1 and OSLER 2 studies, which represented 74.1% of eligible patients in the parent studies, 2976 were randomly assigned to receive evolocumab plus standard therapy and 1489 to receive standard therapy alone. The median duration of follow up was 11.1 months. The mean age of the patients was 58 years. Over 80% had one or more cardiovascular risk factors, such as hypertension, obesity or diabetes. Seventy percent of the subjects were receiving statin therapy at the start of the OSLER trials. Premature, permanent discontinuation of evolocumab occurred in 7.2% of patients.[2,3]

Both trials were designed to have in-person clinic visits on day 1 and then every 12 weeks. OSLER 1 had a duration of 56 weeks while OSLER 2 was designed to last for 48 weeks. At the end of this time period all patients were to receive open-label evolocumab for a longer-term, non-randomized safety and efficacy evaluation.[2,3] The primary end point in the two trials was the incidence of adverse events. Additional safety endpoints included serious adverse events, adverse events leading to the discontinuation of study drug, abnormalities in creatinine kinase levels and liver function tests and the development of binding and neutralizing antibodies against evolocumab. A prespecified exploratory outcome was the incidence of adjudicated cardiovascular events, which was ascertained over the course of the study. Cardiovascular events included death, coronary events, cerebrovascular events, and heart failure requiring hospitalization.[2,3] In addition, all cardiovascular end points except for heart failure were combined into a post-hoc composite of major adverse cardiovascular events.[2,3]

The median baseline LDL-C, before randomization into a parent study, was 120 mg/dL. At the first follow-up visit, 12 weeks into the OSLER trials, evolocumab, as compared with standard therapy, reduced LDL-C level by 61% (95% CI 59-63; P<0.001), for a mean absolute reduction of 73 mg/dL and a median of 48 mg/dL. This decrease in LDL-C was consistent over the course of the trials. At the 12-week point, the LDL-C level was lowered to ≤100 mg/dL in 90.2% of patients and to ≤70 mg/dL in 73.6% of patients in the evolocumab group as compared with 26.0% and 3.8%, respectively, in the standard therapy group.[2,3]

The OSLER trials showed benefits in additional lipid-related laboratory values, such as a 52% reduction in non-HDL cholesterol, 47.3% reduction in apolipoprotein B, 36.1% reduction in total cholesterol, 12.6% reduction in triglycerides, and 25.5% reduction in lipoprotein(a) with evolocumab compared with standard therapy alone (P<0.001 for all comparisons) Evolocumab raised levels of HDL cholesterol and apolipoprotein A1 by 7% and 4.2%, respectively (P<0.001 for both comparisons). All of these lipid changes are expected to be beneficial to cardiovascular health.[2,3]

Cardiovascular events were prospectively adjudicated in an

exploratory analysis. After considering all cardiovascular events observed during these trials, patients in the evolocumab group had a significantly lower rate of all cardiovascular events than did patients in the standard therapy group (HR 0.47; 95% CI 0.28 to 0.78; P=0.003). The cumulative incidence curves diverged progressively over time in the Kaplan-Meier curve. Similar results were obtained during the post-hoc analysis of the OSLER 1 and OSLER 2 trials composite of major adverse cardiovascular events.[2,3]

FOURIER

Currently, a clinical trial is ongoing to investigate the effect of evolocumab on the incidence of major adverse cardiovascular events in patients with clinically evident vascular disease. This study has over 27,000 enrolled subjects at risk for cardiovascular events. The design is a 1:1 randomization of evolocumab or placebo injection in conjunction with standard statin therapy. The primary endpoint of this trial is major cardiovascular events defined as the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization.[2,3]

The results of this trial will hopefully determine whether the addition of evolocumab to statin therapy further reduces cardiovascular morbidity and mortality in patients with vascular disease and could perhaps change the current approach to the treatment of dyslipidemia.

Adverse Events

Adverse events (AEs) occurred in 2060 of 2976 patients (69.2%) in the evolocumab group and in 965 of 1489 patients (64.8%) in the standard-therapy group. A summary of the AEs observed in the OSLER trials can be found in **Table 3**. Serious AEs occurred in 222 patients (7.5%) in the evolocumab group and in 111 patients (7.5 %) in the standard therapy group. There were no concerning elevations in aminotransferase or creatine kinase levels with evolocumab as the two groups had similar rates of adverse events. Although the rate of neurocognitive adverse events was low (<1%), such events were reported more frequently in the evolocumab group. The incidence of neurocognitive adverse events also did not appear to be related to the LDL-C level during treatment. Injection-site reactions were reported in 129 patients (4.3%) in the evolocumab group and led to a discontinuation of evolocumab in 6 patients (0.2%).[1,2] Overall AEs, serious AEs, and elevations in aminotransferase or CK levels were similar in the evolocumab group throughout all LDL-C ranges.[2,3]

Table 3 | Adverse Events and Laboratory Results from OSLER Trials.[3]

Adverse Events	Evolocumab N=2976 (%)	Standard-Therapy N=1489 (%)
Any	2060 (69.2)	965 (64.8)
Serious	222 (7.5)	111 (7.5)
Leading to DC of evolocumab	71 (2.4)	NA
Muscle-related	190 (6.4)	90 (6.0)
Injection-site reaction	129 (4.3)	4 (0.3)
Neurocognitive event	27 (0.9)	4 (0.3)
Other		
Arthralgia	137 (4.6)	48 (3.2)
Headache	106 (3.6)	32 (2.1)
Limb pain	99 (3.3)	32 (2.1)
Fatigue	83 (2.8)	15 (1.0)
ALT or AST >3x ULN	31 (1.0)	18 (1.2)
CK >5x ULN	17 (0.6)	17 (1.1)

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **CK** = creatinine kinase; **DC** = discontinuation; **ULN** = upper limit of normal

Dosing and Administration

The recommended dosing regimens of evolocumab for adjunctive therapy to maximally tolerated statin in patients with heterozygous familial hypercholesterolemia or with established clinical atherosclerosis with primary hyperlipidemia requiring additional lowering of LDL-C are 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously once monthly. The recommended dose for treatment of homozygous familial hypercholesterolemia is 420 mg subcutaneously once monthly.[4] Evolocumab should be administered into the abdomen, thigh or upper arm, and administration sites should be rotated to avoid bruising or tenderness.[4]

Evolocumab should be kept in the refrigerator. The medicine should be warmed to room temperature prior to injection by removing it from the refrigerator for at least 30 minutes. It should not be warmed in any other way besides resting in room temperature. Alternatively to storing in the refrigerator, it may be left in its original carton at room temperature (68°F to 77°F), however, it should be used within 30 days.[4]

Renal and Hepatic Impairment

Evolocumab does not have any specific recommendations for use in patient with severe renal or hepatic impairment. There are also no dose adjustments required for mild to moderate hepatic (Child-Pugh A or B) or renal impairment.[4]

Pregnancy and Breastfeeding

There is currently no data with the use of evolocumab in pregnant women. Limited animal testing was completed which showed no adverse effects in neonatal or infant development at dose exposures up to 12 times the maximum recommended human dose. At birth, newborn monkeys did have measurable evolocumab serum concentrations comparable to concentrations in maternal serum, indicating that evolocumab, like other IgG antibodies, crosses the placenta. Evolocumab appears to cross the placenta at greater concentrations the farther along the pregnancy. The benefits and risks of treatment to the mother and the possible risks to the fetus should be considered before administering evolocumab during pregnancy.[4]

According to the manufacturer, there are no information on evolocumab presence in human milk, on milk production, or effects on a breastfed infant. Human IgG is present in human milk, but data suggests that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. The benefits of breastfeeding, the risk of infant drug exposure, and the risk of an untreated or inadequately treated condition must be weighted before use.[4]

Costs

The U.S. Wholesale Acquisition Cost (WAC) price of Repatha is $14,100 annually. One of the biggest controversies to this point is regarding the cost effectiveness of this medication. There are currently other medications that cost much more than this but they are typically used for a much shorter duration. Current therapies for hepatitis C and some chemotherapies are examples. While these other medications are likely to be used for a few months at most, evolocumab will likely be used on a chronic basis for the duration of an individual's life once prescribed. The economic burden to the current healthcare system is one potential problem for PCSK9 inhibitors.

Current antihyperlipidemic medications are substantially less expensive, but they do not have as large of effects on LDL-C. The upcoming data of health outcomes will likely provide much more clarity as to how much the cost-utility of PCSK9 inhibitors may actually be worth.[6]

The manufacturer, Amgen, does have support services to reduce the copay for Repatha® to as low as $5. Eligibility requirements for the Repatha® copay card include having commercial insurance and applies to deductible, coinsurance, and copay for Repatha®. However, this program is not open to patients receiving prescription reimbursement under any federal, state or government-funded healthcare program.[7]

Summary

PCSK9 inhibitors have the potential to revolutionize current approaches to hyperlipidemia management. The current evidence with evolocumab has shown significant reductions in LDL-C as adjunctive therapies with statins. The key to the clinical implementation is whether these results translate to hard clinical outcomes, such as reductions in cardiovascular morbidity, which still remains to be seen. One potential hurdle this class of medication has to maneuver is the hefty price tag associated with therapy. Ongoing research includes large studies that will soon provide the first evidence regarding the clinical impact of these medications in patients with underlying cardiovascular disease. If results from these trials, such as the FOURIER trial, show drastic decreases in cardiovascular events it may revolutionize the current approach to hyperlipidemia treatment.

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