HHS Public Access

Author manuscript

Headache. Author manuscript; available in PMC 2019 November 01.

Published in final edited form as:

Headache. 2018 November ; 58(10): 1658–1669. doi:10.1111/head.13414.

Recommendations on the Use of Anti-CGRP Monoclonal Antibodies in Children and Adolescents

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Keywords

migraine; calcitonin gene-related peptide; monoclonal antibody; pediatric; adolescent

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Introduction

Migraine is common in children and adolescents and can have long-term consequences on educational performance, self-esteem, and cognitive well-being[1,2]. However, effective, well-tolerated, evidence-based therapies for migraine prevention in children and adolescents remain limited[3].

In adults, monoclonal antibodies (mAbs) to calcitonin gene-related peptide (CGRP), or its receptor, have been shown to be efficacious for migraine prevention [4–11], and in episodic cluster headache [12]. Although CGRP is expressed in multiple body systems[13], trials to date have demonstrated minimal adverse events. The most commonly seen adverse events in adult trials included: injection site reactions, upper respiratory symptoms and constipation. These treatments avoid the need for daily pill taking, and thus may improve adherence, which is known to be low with oral migraine preventives[14].

Pediatric and adolescent migraine prevention trials will follow; however, outcome data from these will likely not be available for several years. In the interim, the decision regarding whether to treat pediatric patients with anti-CGRP mAbs will require providers to balance the potential for unknown risks against the potential benefits of the therapy. To bridge the gap until empiric data become available, this manuscript, written by members of the Pediatric & Adolescent Headache special interest group of the American Headache Society, is meant to serve as expert opinion, i.e. class IV evidence, on the use of these antibodies in children and adolescents. This topic was discussed at the Pediatric & Adolescent Headache special interest group (SIG) meeting at the 2018 Annual Scientific Meeting of the American Headache Society, and via email communication to SIG members. Interested members volunteered to collaborate as co-authors on this document. Authors divided into subgroups to draft the various sections of the manuscript. Recommendations were reached by consensus first within the subgroups and then all co-authors had the opportunity to read the entire manuscript so that final recommendations could be reached by consensus. The opinions expressed in this manuscript represent those of the co-authors and do not represent the opinion of the American Headache Society.

What we know about the use of monoclonal antibodies in children and adolescents

Monoclonal antibodies (mAbs) have been used to treat a range of pediatric disorders for two decades. These disorders include multiple sclerosis, autoimmune encephalitis, inflammatory bowel disease, systemic lupus erythematosus, juvenile idiopathic arthritis, oncologic disease, and others[15]. Monoclonal antibodies require parenteral administration, usually intravenous, subcutaneous, or intramuscular. They are degraded via three major routes: extracellular proteolysis mainly via proteases, target-mediated elimination, and intracellularly[15]. They do not interact with the cytochrome P450 system[16], thus dose adjustments for hepatic and renal impairment are not required.

Pediatric dosing for mAbs is often extrapolated from adult doing based on body surface area (BSA) or weight, and age. When dosed based on weight and age, younger children tend to

have faster plasma clearance and thus lower plasma concentrations and peak concentrations[15]. However, when dosing is based on BSA, younger children may have higher plasma exposures than adults as they have a higher surface area to volume ratio. Therefore, approved pediatric mAb dosing approaches include tiered fixed dosing which are staggered based on weight, weight-adjusted and hybrid dosing[17]. Pediatric pharmacokinetic studies of anti-CGRP mAbs are planned or ongoing. For estimation, 1mg/kg of IgG is only about 0.1–0.2% of the body's IgG content (at least in adults), so mAbs used for migraine represent only a small fraction of the body's total antibodies[18]. In adult subjects the half-lives of the anti-CGRP mAb range from 21 to 50 days[19].

Safety and potential immunogenicity of mAbs relate to antibody type and the proportion of non-human or foreign sequences they contain, whether chimeric (-xi-), chimeric/humanized (-xizu-), humanized (-zu-), or fully human (-u-)[16]. All 4 of the anti-CGRP mAbs which have been studied for migraine prevention are Immunoglobulin G (IgG) based[20], and are not expected to cross the blood brain barrier[19]. Erenumab is fully human, whereas galcanezumab, fremanezumab, and eptinezumab are humanized antibodies. Fully human and humanized antibodies may reduce the risk of marked immunogenicity, though immune reactions can still occur[21]. Serious infections are rare even with immunosuppressive mAbs[22].

CGRP Physiology and corresponding clinical recommendations regarding monitoring of children and adolescents receiving anti-CGRP mAbs:

CGRP is found primarily in unmyelinated aδ and C sensory nerve fibers, but also has a wide distribution in the central nervous system and in non-neuronal tissues throughout the body[19,23]. The known physiological roles of CGRP are numerous[23,24] and extend far beyond its established role in the pathophysiology of migraine. Given that children and adolescents with migraine appear to have elevated CGRP levels as compared to controls, at least during attacks[25], it is unclear whether the anti-CGRP mAbs would reduce CGRP levels to a subnormal level that could impact various physiological processes or whether the magnitude of the reduction would simply restore levels to within the normal physiologic range. If the latter is true, the impact on tissues could be minimal.

Central & Peripheral Nervous System:

CGRP and its receptors are expressed in significant concentrations during postnatal animal brain development[26,27] and are likely involved in central nervous system maturation[27,28]. CGRP may also play a role in nervous system recovery after injury [29,30]. Anti-CGRP mAbs may not have a significant impact on central nervous system development (CNS) given that they are unlikely to penetrate the blood-brain-barrier in significant concentrations under physiologic conditions[19,31]. However, it might be possible that by siphoning off CGRP in the periphery the anti-CGRP mAbs could lead to a central reduction in CGRP through a "sink phenomenon", as has been postulated with other peripherally-acting mAbs" [32,33]. If peripheral binding of CGRP by monoclonal antibodies is capable of reducing central CGRP levels, there could potentially be an effect on brain development.

Clinical Recommendation: Until more data are available we recommend against use in children or adolescents with a potentially compromised blood-brain barrier (e.g. those with recent meningitis, neurosurgery, or central nervous system injury such as stroke) or recent peripheral nerve injury.

Maintenance of Pregnancy and Fetal Development:

CGRP appears to play a key role in utero-placental functions[34,35], and vascular adaptations to pregnancy[34–36]. In human pregnancies complicated by pre-eclampsia, the normal CGRP-induced vascular relaxation is impaired[37]. IgG type antibodies cross the human placenta[38]. Maternal-fetal IgG transfer is limited before the 16th week of gestation, and rises rapidly after week 22[39], hence anti-CGRP antibodies could impact the developing fetus particularly in the second and third trimester. Pregnant rats exposed to a CGRP antagonist had pups with restricted growth or fetal demise[34]. CGRP receptor component knockout mice experience hydrops fetalis and die in utero[36]. Given that few pregnant women were exposed to anti-CGRP mAbs during the adult trials, data on human pregnancies are minimal.

Clinical Recommendation: Based on the available data at this time, anti-CGRP mAbs should not be prescribed to adolescent or adult females known to be pregnant, breastfeeding, or planning to become pregnant within the next 6 months. Clinicians should counsel female patients who have reached menarche about the possible teratogenic effects and other possible negative pregnancy outcomes that could result from blocking the CGRP pathway, and continue to discuss pregnancy avoidance during the course of care. Clinicians should consider pregnancy testing if it is their usual practice to do so prior to prescribing migraine preventives which are known to be teratogenic[40,41].

Bone:

In animal models, CGRP has been implicated in stimulating bone formation and ossification[42–45]. Mouse models in which the α-CGRP gene is knocked out have yielded animals with decreased bone mass[43]. CGRP monoclonal antibodies could theoretically impact linear growth and/or bone mass if CGRP does play a role in bone development in humans. However, at the present time we are not aware of human data on this topic. This may be relevant throughout adolescence, as 40 to 60% of adult bone mass is acquired during that time. Approximately 25% of adult bone mass is acquired during peak height velocity growth[46], which typically occurs at 12.5 years for girls and 14 years for boys[47]. By age 18, 90% of peak bone mass has been attained[48].

Clinical Recommendation: Based on the available data at this time, anti-CGRP mAbs should be used with caution in children and adolescents with known bone diseases or significant osteopenia. Clinicians should carefully monitor height and linear growth in children and adolescents receiving anti-CGRP mAbs, and consider waiting to prescribe until the child is post-pubertal. Vitamin D level optimization would be a relatively non-invasive way to support healthy bone growth.

Metabolism:

There is evidence from animal models that CGRP modulates glucose-stimulated insulin release. As compared to wild-type mice, α-CGRP knockout mice fed a high-fat diet for several weeks had more favorable glucose handling and insulin sensitivity and decreased body weight[49]. Both animal[50] and human[51] data suggest that obesity may be associated with elevated CGRP levels. If CGRP is involved in human weight regulation, then anti-CGRP monoclonal antibodies may lead to decreased weight and thus baseline body mass index (BMI) of the child or adolescent might be a consideration. However, a significant effect on body weight has not been reported in adult migraine trials to date. Another consideration is CGRP expression in the anterior pituitary. The pituitary gland is outside the blood-brain-barrier[52,53], and anti-CGRP mAbs could theoretically affect pituitary function[13], such as by reducing growth hormone secretion[54].

Clinical Recommendations: Monitor weight and BMI in children and adolescents receiving anti-CGRP mAbs. While there is no evidence that pituitary hormones need to be monitored in all children and adolescents receiving these antibodies, if suggestive symptoms arise, consider laboratory testing to evaluate pituitary function.

Immune System:

CGRP plays a role in the neuro-immune axis, with CGRP-containing nerve fibers located in the thymus, bone marrow, spleen, skin, lymph nodes, lungs and gastrointestinal tract[55]. CGRP receptors are present on lymphocytes, macrophages, mast cells and dendritic cells, and, in turn, these cells can synthesize CGRP[55]. CGRP exerts a variety of pro- and anti-inflammatory actions, and is hypothesized to exert nervous system control over immune function[55]. Reassuringly, adult participants in trials to date have not developed serious infections.

Clinical Recommendation: Consider avoiding anti-CGRP mAbs in children and adolescents with known immunodeficiency or who are receiving immunosuppressive medications, and cease therapy if serious or recurrent infections develop.

Cardiovascular system:

CGRP is a potent vasodilator, and has a significant presence in the cardiovascular system and in perivascular nerves[23]. Adult studies have not found any significant effect of anti-CGRP mAbs on exercise in patients with stable angina[56], nor on blood pressure, even with concomitant sumatriptan use[57]. However, open questions remain about the cardiovascular effects of blocking CGRP[58].

Clinical Recommendations: Consider avoiding use in those with structural heart defects, cardiomyopathy, pulmonary hypertension, coronary artery disease (from conditions such as Kawasaki's), and history of or significant risk factors for stroke.

Recommendations on when to consider clinical use of anti-CGRP mAbs in children and adolescents with migraine:

Given the relative unknowns, until studies in children and adolescents are completed, anti-CGRP mAbs should be considered primarily for post-pubertal adolescents experiencing relatively frequent migraine (i.e. ≥8 headache days per month) with moderate or severe migraine-related disability (as measured by PedMIDAS or other validated instrument). In the event that a younger child has severe chronic migraine that has proven refractory to multiple migraine preventive trials, it would be reasonable to consider anti-CGRP mAb therapy with careful monitoring as described above.

In order to justify taking on the possible risks of the anti-CGRP mAbs in this population, patients should have had adequate trials of, or contraindications to, established migraine preventive therapies. How many preventives should be tried first is a matter of clinical judgement and the authors of this manuscript had varied recommendations between two and three prior preventives. Some insurance companies may require patients to have trialed at least two prescription preventive medications that are deemed to have Level A evidence for migraine prevention in adults[59]. Given that the Childhood and Adolescent Migraine Prevention (CHAMP) trial demonstrated similar rates of improvement in children and adolescents treated with placebo as with prescription preventives[60], we recommend that in these age groups **the options for previous preventive treatment trials be expanded beyond prescription preventive medications to include, though not require, trial of** cognitive behavioral therapy, which is well-supported by evidence[61–63], as well as treatments that have fewer side effects such as neuromodulation devices[64] and supplements (riboflavin, Coenzyme Q10, magnesium, and melatonin)[65–73].

Treatment trials of anti-CGRP mAbs in adults have demonstrated efficacy within the first two months of treatment, with therapeutic gains remaining stable over 6 months[74,75]. Open label extension trials have demonstrated some gains at the one-year mark[74]. Previous pediatric migraine studies have demonstrated that patients who initially improve with treatment are likely to maintain this improvement[76,77]. The natural course of migraine may be more easily improved in the developing brain[78], potentially allowing for shorter treatment duration. Given the above, and the unknowns of long-term use of the anti-CGRP mAbs particularly in the developing patient, we recommend an initial two-month trial at the lowest available dose. If no improvement is seen, a higher dose may then be trialed for another two months. If there is still no benefit with the higher dose, or it is not tolerated, the medication should be stopped. If improvement is seen, we recommend continuing the medication in an attempt to reach a patient-centered overall treatment goal of fewer than one headache per week[79]. If this goal is attained, the patient can be continued on the medication for another few months and then efforts should be made to wean off the medication[80].

Recommendations regarding participant selection for anti-CGRP mAb trials in pediatric and adolescent migraine

In the past 15 years, migraine preventive trials in children and adolescents have demonstrated that a substantial proportion of children and adolescents assigned to the placebo arm have a clinically meaningful improvement in headache frequency[3,81–83]. Placebo response has a number of potential biological and psychological mechanisms and is an important area of scientific investigation in its own right[84–87], and knowledge of its potential magnitude is important in designing clinical efficacy trials. In the case of pediatric and adolescent trials of anti-CGRP mAbs it is possible that placebo response rates could be even higher than what has been seen in oral preventive trials as work in adults has demonstrated that placebo response rates to injections are higher than to oral medications[88–90]. In addition, as at least one anti-CGRP mAb has already received US FDA approval for adults, the placebo response may be increased by participants' high expectation of benefit[91].

Novel approaches to trial design for pediatric and adolescent migraine prevention are needed in order to allow separation of placebo from active treatment, if indeed there is biologic efficacy of anti-CGRP monoclonal antibodies in these age groups above that which is provided by placebo. Trial design options include:

1. *Single-blind placebo run-in*: i.e. all participants initially receive placebo and then only those who do not respond are randomized. In pediatric and adolescent triptan trials, those in which subjects were given a single-blind placebo run-in treatment and only non-responders were randomized, were successful in demonstrating efficacy[92–94]. This design has been used in adult migraine research[95], and is being implemented in at least one pediatric migraine preventive trial[96]. It enriches for participants who are either more refractory or those who have a lower "expectation" of response. Though the optimal duration of placebo run-in for an injection-based therapy is not known, data showing trajectory of improvement from recent pediatric trials would suggest that 8-weeks would be adequate at least for oral therapies [77,97].

2. *Crossover design*: i.e. the same participants are alternately treated with both placebo and the experimental treatment. This has the advantage of using participants as their own controls. However, data from CHAMP demonstrated that benefits from preventive therapy can persist for over 12 months [97], making crossover designs impractical for pediatric and adolescent migraine prevention studies.

3. *Limit enrollment to participants who have not responded to previous trials of migraine preventive therapies*: Adult studies of anti-CGRP antibodies have demonstrated a larger therapeutic gain (i.e. difference between active and placebo) among participants who had been refractory to ≤4 prior preventive medications[98,99]. This was driven predominantly by a reduced placebo response, which may be due to a lower expectation of response in this group. From a practical standpoint, previous preventive trials are likely to be required by

insurance companies before approval is given for more expensive agents. However, results would not necessarily generalize to all children and adolescents with migraine and may therefore limit FDA-approval to patients who have previously failed other preventives.

Regardless of which study design is chosen, we recommend that children and adolescents with continuous headache *not* be excluded, as these are the patients most in need of novel therapeutics[100]. Primary and secondary endpoints should reflect those recommended in the International Headache Society's guideline for controlled trials[101], and should be collected using the NIH's recommended Common Data Elements[102]. Monitoring should mirror what was done in adult trials, with the addition of monitoring growth. Given that this is a novel therapeutic class in humans, we recommend consideration of long-term outcome registries for those who are exposed to these treatments as children and adolescents[103].

Use of anti-CGRP mAbs in children and adolescents with other headache disorders

Cluster Headache

Cluster headache (CH) [104] is a severe, relatively rare primary headache [105] disorder[106]. CH clearly occurs in children and adolescents [107–109]; though clinically it seems less common than in adults, although this has not been systematically tested.

The rationale for the use of anti-CGRP pathway monoclonal antibodies in CH comes from supportive basic science and three lines of experimental medicine. CGRP is found in the trigeminovascular system [110,111], which is part of the basis for its role in migraine [112]. CGRP is released into the cranial circulation during acute spontaneous [113] and nitroglycerin-induced [114] CH. Moreover, CGRP can trigger CH when patients are in bout [115], although not when they are out of bout [116], indicating that both peripheral and central mechanisms may be involved in CH pathophysiology. Most recently results of a randomized placebo-controlled trial in adults with episodic cluster headache demonstrated that galcanezumab was superior to placebo in reducing mean weekly cluster attacks. Some three-quarters of patients treated with galcanezumab had a ≥ 50% reduction in attacks [12].

The relative rarity of CH in adolescents will make a well-powered placebo controlled trial difficult to execute. However, the inherent pain severity described in this population argues for its use in this age group based on the adult study. If anti-CGRP mAbs are approved for CH in adults, one could argue for allowance of use in children and adolescents with CH followed by a registry.

New Daily Persistent Headache (NDPH)

New daily persistent headache (NDPH) [104] seems to be more common in children and adolescents as compared to adults[117]. There is a paucity of evidence to guide treatment of NDPH in adults, children and adolescents[118], thus treatments are typically geared toward the phenotype (migraine versus tension-type)[118,119]. Given the known efficacy of anti-CGRP monoclonal antibodies in chronic migraine[9–11], it would be reasonable to treat NDPH of a migrainous phenotype with these agents as well.

Persistent headache attributed to traumatic injury to the head

Chronic post-traumatic headache (PTH) [104] is a common secondary headache seen in the pediatric population[120]. CGRP has been reported to be released in PTH[121], and found to be elevated in the trigeminal nucleus caudalis of those who have suffered repeated head injuries[122]. While PTH is a secondary headache, its phenotype often resembles that of migraine, and there may be overlapping pathophysiology. As with NDPH, there are no studies to date looking at anti-CGRP monoclonal antibodies for the treatment of persistent PTH. However, for those patients with persistent PTH of a migrainous phenotype who have not responded to conventional therapies, it may be reasonable to try anti-CGRP monoclonal antibody treatment.

Access to anti-CGRP monoclonal antibodies

The prevalence of migraine, and chronic migraine, is higher among children from lower socioeconomic backgrounds compared to their more affluent peers[123]. Similarly, adolescents with a household income of < $22,500 per year have a migraine prevalence nearly double that of adolescents with a household income > $90,000 per year [124]. Yet children and adolescents from lower socioeconomic backgrounds are also more likely to be uninsured or under-insured. In one study, 22% of individuals in working poor families were uninsured compared to only 5% in moderate to affluent families[125]. Access and quality of healthcare is often suboptimal for uninsured or underinsured pediatric patients[126]. Many of these children rely on community clinics and county or city hospitals for their migraine management; these facilities may not have child neurologists or pediatric headache specialists[127].

Given that migraine is a treatable cause of missed school and impaired performance at school[123,128,129], it is imperative that clinicians advocate for equality of access to migraine therapeutics for children and adolescents, whether the intervention is a prescribed medication, a device, or non-pharmacologic therapy. The passage of the Best Pharmaceuticals Act for Children (BPCA) and the Pediatric Research Equity ACT (PREA) has resulted in increased evaluation and FDA labeling of drugs in children through the pharmaceutical industry and through government sponsored trials[130]. However, pediatric labeling still exists for fewer than 50% of products[131]. This results in “off-label” drug use being common practice in the care of pediatric patients. The absence of FDA labeling for a specific age group or for a specific disorder does not imply that the drug’s use is improper for that age or disorder, but that the evidence required by law to allow inclusion of that group in the label has not yet been obtained[130]. Well-designed trials of the anti-CGRP monoclonal antibodies for migraine prevention in children and adolescents are needed not only to allow practitioners to make informed therapeutic decisions, but also to allow better access to, and insurance coverage of, these medications in this age group. In the meantime, clinicians will need to advocate for patients who need access to these therapies today, despite the high price-tag.

Conclusions

Anti-CGRP mAbs have been shown to be effective for migraine prevention in adults and have not raised major safety issues, though long-term safety data are not yet available.

Pediatric and adolescent trials of anti-CGRP mAbs should be designed to maximize the chances of determining efficacy in these age groups, and should focus on those who have not been successful with current multidisciplinary care. In the interim, the use of anti-CGRP mAbs for the treatment of headache disorders in children and adolescents may be considered in appropriate cases, but should be done with close follow-up and attention to patient characteristics such as age, pubertal state, and medical comorbidities.

Acknowledgments

Financial disclosures:

CS: Has received grant support from Pfizer and Amgen.

JVP: reports speaking fees for Amgen and Novartis, and consulting for Healint.

SLO: Receives royalties from Cambridge University Press

CO: None

WQ: None

IP: none

AMLB: Is on the advisory board for Teva, Novartis and Allergan and the speakers' bureau for Aralez.

CM: None

JG: Speaker's bureau for Supernus and has received travel funds from the American Academy of Neurology.

MCV: Has received travel funds from the American Academy of Neurology and honoraria for authorship from Merck.

SH: none

MC: none

CC: none

RR: none

RHF: Receives funding from the National Institutes of Health.

AB: none

MY: Has received consulting fees from Amgen, Impax, Upsher-Smith, and Avanir

ADH: Alder, Amgen, Curelator, Depomed, Electrocore, Impax, Lilly, Teva and Upsher-Smith

SWP: Receives funding from the NIH

PJG: PJG reports grants and personal fees from Amgen and Eli-Lilly and Company, and personal fees from Alder Biopharmaceuticals, Allergan, Autonomic Technologies Inc., Dr. Reddy's Laboratories, Electrocore LLC, eNeura, Novartis, Scion, Teva Pharmaceuticals, and Trigemina Inc., and personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press, Massachusetts Medical Society, and Wolters Kluwer; and a patent Magnetic stimulation for headache assigned to eNeura without fee.

AAG: Has received consulting fees from Zosano, Eli Lilly, Impax and Biohaven. She has received honoraria from UpToDate (for authorship) and JAMA Neurology (as an associate editor). eNeura provides consulting payments for work done by Dr. Gelfand to the UCSF Pediatric Headache program. She receives personal compensation for medical-legal consulting. Her spouse receives consulting fees from Genentech, research support from Genentech, Quest Diagnostics and MedDay, and personal compensation for medical-legal consulting.

Funding:

Dr. Szperka receives research funding from the National Institute of Health (K23NS102521). There was no specific funding for this project.

Abbreviations:

CGRP	calcitonin gene-related peptide
mAb	monoclonal antibody, anti-CGRP
mAb	a monoclonal antibody that targets CGRP or its receptor
CNS	central nervous system
BSA	body surface area
BMI	body mass index
NDPH	New Daily Persistent Headache
CH	Cluster Headache

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Table 1.

Suggested indications, contraindications and monitoring for use of CGRP monoclonal antibodies in children and adolescents with migraine

Indications	**Contraindications**	**Monitoring**
• ≥8 headache days per month • PedMIDAS score ≥30 • Failure of ≥2 preventive therapies (pharmacologic, nutraceutical, and/or non-pharmacologic) • Post-pubertal adolescent, or pre-pubertal child in selected cases	• Disturbed blood-brain barrier (e.g. recent history of meningitis, recent neurosurgery) • Severe cardiovascular disease, stroke • Pregnancy, planned pregnancy or breast-feeding	• Pubertal status • Bone health, consider checking Vitamin D status • Linear growth • Weight/BMI • Infections • Pregnancy status

BMI=body-mass index