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Expert Opinion

Raynaud's Phenomenon Associated With Calcitonin Gene-Related Peptide Monoclonal Antibody Antagonists

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Two cases are reported of migraineurs who reported Raynaud's phenomenon (RP) exacerbated while taking monoclonal antibodies to the calcitonin gene-related peptide (CGRP) ligand (fremanezumab and galcanezumab) and 1 case of new onset RP while taking the CGRP receptor antagonist (erenumab). The prevalence of primary and secondary RP, causes of secondary RP, co-morbidity with migraine, and medications which might induce or exacerbate RP are reviewed. The pathophysiology of how CGRP monoclonal antagonists might exacerbate or induce RP is discussed. The cases suggest but do not prove causation.

Key words: migraine, Raynaud's phenomenon, erenumab, fremanezumab, galcanezumab

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Maurice Raynaud's (1834-1881) doctoral thesis as a medical student at the University of Paris in 1862 was titled, "Local asphyxia and symmetrical gangrene of the extremities."[1] He described 25 patients, 20 females, with a series of color changes in the hands and feet when exposed to the cold or when under stress.[2] Raynaud's phenomenon (RP) usually begins in a single finger and then spreads to other fingers symmetrically in both hands most frequently the index, middle, and ring finger often sparing the thumb.[3] When the thumb is involved, a secondary cause of RP may be present. Secondary RP has many possible causes including medications. RP can be triggered by exposure to cold temperature (including changes from warmer temperature to air conditioning or the refrigerated section of the grocery store), emotional stress, and sudden startling.[4]

The following 3 cases describe monoclonal antibodies to CGRP associated with an exacerbation of pre-existing RP in 2 cases and 1 associated with new onset RP.

CASE HISTORIES

Case 1.—This is a 45-year-old female with a 20 year history of migraine without aura occurring twice a week treated with rizatriptan. She had failed 2 preventives. She was taking no other medications. Past medical history was negative except for a history of occasional RP 10 years prior when she lived in a much colder climate. She had no evaluation for secondary RP. Neurological exam was normal.

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Conflict of Interest: Allergan [Migraine (Botulinum toxin)]; Amgen [Migraine (Erenumab-aooe)]; Avanir [Migraine (Sumatriptan nasal powder)]; Depomed [Migraine (Diclofenac potassium)]; Depomed [Postherpetic neuralgia (Gabapentin)]; electroCore [Migraine and cluster headaches (gammaCore)]; Novartis [Migraine (Erenumab-aooe)]; Promius [Migraine (Sumatriptan)]. Consultant/Advisory Boards: Alder [Migraine (Eptinezumab)]; Egalet [Pain (Ketorolac tromethamine)]; Eli Lilly [Migraine (Galcanezumab)]; Teva [Migraine (Fremanezumab)].

She was given a loading dose of galcanezumab 240 mg sc in November, 2018. When seen for follow-up 3 months later, she reported having 2 headaches; the first, couple of days after receiving galcanezumab and then none until 2 in the prior week.

On February 7, 2019, she reported that she had frequent and more severe RP (the thumb was not involved) including mild digital ulcers (which had healed by the time of the visit) for about 1 month after receiving galcanezumab. She did not give herself any further injections with no further episodes of RP.

Case 2.—This is a 65-year-old male with a history of migraine since his teens which have been chronic and daily for many years not responsive to many preventive agents. Past medical history of hypertension, coronary artery disease post stent 17 years prior, hyperlipidemia, and occasional RP which would variably affect the second, third, and fourth fingers only, sometimes only a single finger at a time. He had no evaluation for secondary RP. Medications included atorvastatin, candesartan, ezetimbe, and aspirin.

He was started on fremanezumab in early November, 2018. With onset a few weeks after injection, he began to have frequent episodes of RP involving all the fingers of both hands in cool temperatures. Starting 3 months after injection, the headaches decreased to every other day and were less intense and he chose to continue the fremanezumab.

Case 3.—This is a 33-year-old female with migraine without aura since age 13 with migraine for years occurring about 15 days per month. She had failed many preventive medications. She was seen on February 20, 2019 after having injected erenumab 140 mg sc monthly for 7 months with a greater than 50% reduction in migraine days.

She reported that in November and January when outside in the cold for about 1 hour, she had RP of all the fingers and toes bilateral with temperature change and numbness lasting about 1 hour after going indoors and taking a hot shower. She has no other episodes of being in the cold for prolonged periods. No other or prior history of RP and no evaluation for RP. Past medical history of anxiety. Other medications included sumatriptan 6 mg sc or rizatriptan 10 mg sc prn, baclofen 10 mg tid prn headache, buspirone 15 mg bid, ondansetron 8 mg tid prn, and medroxyprogesterone acetate.

Questions.—What is the prevalence of primary and secondary RP in the general population? What are secondary causes of RP? Is RP co-morbid with migraine? Could monoclonal antibodies against calcitonin gene-related peptide (CGRP) exacerbate or cause RP? Are there other medications used for migraine which can induce RP?

EXPERT OPINION

The Prevalence of Primary and Secondary Raynaud's Phenomenon.—Primary RP usually has an age of onset between 15 and 30 years of age and is more common in women but occurs later in life including a prevalence of new-onset RP in 0.1 to 1% of people over 60 years of age.[5]

In community-based surveys, the prevalence of RP has ranged from 3 to 20% in women and 3 to 14% in men with geographic variability.[5] In 6 cross-sectional studies in the general population, the overall prevalence of definite primary RP varies from 2.1 to 15.8% in women and 0.8 to 6.5% in men.[6] In 3 cross-sectional studies, the overall prevalence of possible primary RP ranged from 4.5 to 17.9% in women and 3.4 to 7.2% in men.

In the Framingham Study of a general population cohort of 4182 people followed for 16 years, the prevalence of primary RP was 9.6% in women and 8.1% in males with 81.4% of cases primary.[7] The most common causes of secondary RP were beta-blocker use (34.2%), carpal tunnel syndrome (10.5%), and rheumatoid arthritis (7.2%).

In a prospective follow-up study of 244 patients with primary RP, 236 were followed for a mean of 11.2 ± 3.9 years. The annual incidence of transition to suspected secondary RP was 1%.[8]

Secondary Causes of Raynaud's Phenomenon.—The following are secondary causes of RP: connective tissue diseases (scleroderma, systemic lupus erythematosus, mixed connective tissue disease, and Sjögren's syndrome) vascular diseases (atherosclerosis, subclavian artery stenosis, giant-cell arteritis, nodular arteritis, Takayasu's disease, Behçet's disease, and trauma); various drugs or toxins (see last question); hematologic abnormalities (cryoglobulinemia, cold agglutin

disease, paraproteinemia, cryofibrinogenemia, and POEMS [polyneuropathy, organomegaly, monoclonal gammopathy, and skin changes]); infectious (diseases (hepatitis B and C and leprosy); occupational and environmental (use of vibrating tools, pianists, typists, and frostbite); hypothyroidism; and neurological disorders (syringomyelia, multiple sclerosis, migraine, carpal tunnel syndrome, thoracic outlet syndrome, multiple system atrophy, polymyositis, and Sneddon's syndrome.[4,9]

Raynaud's Phenomenon is Co-morbid With Migraine.—In a study of 111 migraine patients and 111 controls matched for age and sex in Israel, the prevalence of RP was 26% in migraineurs and 6% in the control population.[10] The prevalence of RP in those with classic migraine (migraine with aura) was 33% compared to 22% in those with common migraine (migraine without aura; P not significant). The difference in the prevalence of RP in women (23%) and men (34%) were not significantly different.

In a survey in Massachusetts at a Raynaud's disease clinic, 61% of 93 patients had migraine compared to 23% of 93 age-and sex-matched controls without RP.[11] In a random survey of 41 subjects identified with RP in a random survey of hospital employees in Massachusetts, migraine was present in 58.5% with RP compared to 24.4% of a group matched for sex and age without RP.[12]

In a study of primary RP subjects with 4 candidate vasoactive mediator genes, 32.6% had migraine compared to 7.2% of a normal control population.[13] There were no significant differences in allele frequencies of the candidate genes between the migraine and control groups. The findings do not suggest that common molecular variants of these candidate genes are involved in primary RP.

In a study of 756 employees of a hospital in Greece, 26 subjects were found to have primary RP including 12 (46.2%) with migraine.[14] In a study of 1414 healthy Turkish medical students and hospital personnel, there was no significant difference in the prevalence of RP in those with migraine (9.8%) vs those without migraine (7.8%).[15]

Combining these 6 studies,[8] migraine had a pooled odds ratio of primary RP of 4.02 (95% CI 2.62 to 6.17). The pathophysiology of the co-morbidity is not known.

Could Monoclonal Antibodies Against CGRP Exacerbate or Cause RP?—The 3 cases present suggest but certainly do not prove that monoclonal antibodies against CGRP might exacerbate or cause RP. Each person was taking 1 of the 3 available monoclonals including the 2 which block the ligand (galcanezumab and fremanezumab) and 1 which blocks the receptor (erenumab). The involvement of the thumbs with the RP in cases 2 and 3 suggest secondary RP.[16]

There is a balance between vasodilation and vasoconstriction in nerve endings in the peripheral nervous system which sense the microenvironment and release neuropeptides.[17] Vasodilators released are substance P, vasoactive intestinal peptide, CGRP, and neurokinin A and vasoconstrictors released are somatostatin, and neuropeptide Y.

In a study comparing skin biopsy samples from the fingers of 9 patients with primary RP, 9 RP associated with systemic sclerosis, and 11 healthy controls examined with immunocytochemistry, there was a significant reduction in the number of CGRP immunoreactive neurons in the skin of patients with primary RP and those with systemic sclerosis compared to controls.[18]

Clinicians may wish to observe for the presence of possible exacerbation of inducement of RP in migraineurs receiving monoclonal antibodies against CGRP.

Are There Other Medications Used for Migraine Which can Induce or Exacerbate RP?—There are 12 classes of drugs which may be responsible for RP with a variety of underlying mechanisms as follows: drugs enhancing vasoconstriction (beta-adrenergic blockers, clonidine, ergot alkaloids, dopaminergic agonists, selective serotonin reuptake inhibitors [SSRIs], stimulants, cyclosporine, sympathomimetics, and toxic substances [cocaine]); endothelium damage and/or neurotoxicity (including cis-platinum, bleomycin, and vincristine); occupational and/or environmental exposure (vinyl chloride); drugs increasing blood viscosity and enhancing vasoconstriction (interferons); and unknown mechanism (tyrosine kinase inhibitors, fluorescein, sulfasalazine, propofol, amphotericin B, iloprost, and yohimbine).[19]

Medications used for migraine can induce RP. In the Framingham study, the most common cause of

secondary RP was beta-blocker use (34.2%).[9] In a meta-analysis of 13 studies, the prevalence of RP in those receiving beta-blockers was 14.7%.[20]

In small studies, there was no worsening in the symptoms of pre-existing RP given beta-blockers.[21,22] The Lexicomp drug information for propranolol states: "Peripheral vascular disease (PVD) and Raynaud disease: Can precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud disease. Use with caution and monitor for progression of arterial obstruction."[23] The risk of significant harm of administering beta-blockers to migraineurs is not known as anecdotally, beta-blockers are often prescribed without obtaining a history of RP.

Ergotamine and dihydroergotamine (DHE) are weak peripheral blood vessel constrictors at therapeutic doses.[19] It is not clear to what degree, if any, they might exacerbate pre-existing RP in migraineurs. The rare adverse event of prolonged peripheral vasoconstriction caused by ergots, "ergotism," with an estimated incidence of 0.1% might be interpreted as RP.[19] Ergotism can occur with overdosing the ergot or when using other drugs which are metabolized by the liver such as antibiotics, oral contraceptives, protease inhibitors and combined use with beta blockers. Smoking and caffeine increase the risk of ergotism.[24] In a study of 114 chronic migraineurs given a 5-day regimen of intravenous DHE, an exacerbation of RP is not listed as an adverse event.[25]

According to the package inserts for triptans, RP is listed as an adverse event with a frequency not defined.[26] However, a PubMed search does not find any cases reported. In a comprehensive review of drug-induced RP, Khouri et al state, "… other drugs targeting serotonin receptors such as triptans, selective agonists of 5-$HT_{1B/1D,}$ do not induce vasoconstriction of extremities and RP."[19]

In the Lexicomp drug information for ergotamine, cold extremities are listed as an adverse reaction with frequency not defined.[27] PVD is listed as a contraindication to use but there is no specific mention of RP. In the Lexicomp drug information for DHE, peripheral cyanosis is listed as a <1% adverse event in postmarketing and/or case reports. Under warnings/precautions, "May cause vasospastic reactions associated with symptoms of muscle pains, numbness, coldness, pallor, and cyanosis of the digits …: and " … evaluate patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome."[28]

SSRIs are sometimes used for migraine prevention. There are contradictory reports of the effects of SSRIs on peripheral vasoreactivity. For example, there is a report of treatment of RP with fluoxetine[29] and another report of fluoxetine inducing RP.[30]

CONCLUSION

RP is common occurring in up to 20% of women and 14% of men and is more common in migraine with an odds ratio of 4.02. There are many secondary causes of RP including 12 classes of drugs.

Two cases are reported of migraineurs who reported RP exacerbated while taking monoclonal antibodies to the CGRP ligand (fremanezumab and galcanezumab) and 1 case of new onset RP while taking the CGRP receptor antagonist (erenumab). It is possible that CGRP antagonism may be causal especially as a small study found a significant reduction in CGRRP immunoreactive neurons in the skin of the fingers of patients with primary RP. Further case reports and studies of exacerbation or induction of RP in patients taking these monoclonal antibodies will be of interest.

REFERENCES

1. Raynaud M. *De l'asphyxie locale et de la gangréne symétrique des extrémitiés*. Paris: Rignoux; 1862.
2. Prabhu AV, Oddis CV. The legacy of Maurice Raynaud. *JAMA Dermatol*. 2016;152:1253.
3. Chikura B, Moore TL, Manning JB, Vail A, Herrick AL. Sparing of the thumb in Raynaud's phenomenon. *Rheumatology (Oxford)*. 2008;47:219-221.
4. Wigley FM. Clinical manifestations and diagnosis of the Raynaud phenomenon. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. Available at: https://www.uptodate.com. Accessed February 24, 2019.
5. Ling SM, Wigley FM. Raynaud's phenomenon in older adults: Diagnostic considerations and management. *Drugs Aging*. 1999;15:183-195.
6. Garner R, Kumari R, Lanyon P, Doherty M, Zhang W. Prevalence, risk factors and associations of primary Raynaud's phenomenon: Systematic review and

meta-analysis of observational studies. *BMJ Open*. 2015;5:e006389.
7. Brand FN, Larson MG, Kannel WB, McGuirk JM. The occurrence of Raynaud's phenomenon in a general population: The Framingham Study. *Vasc Med*. 1997;2:296-301.
8. Hirschl M, Hirschl K, Lenz M, Katzenschlager R, Hutter HP, Kundi M. Transition from primary Raynaud's phenomenon to secondary Raynaud's phenomenon identified by diagnosis of an associated disease: Results of ten years of prospective surveillance. *Arthritis Rheum*. 2006;54:1974-1981.
9. Kaluzny K, Brola W, Fudala M. Zespół Raynauda w chorobach neurologicznych [Raynaud's phenomenon (syndrome) in neurological disorders]. *Med Rev*. 2013;4:536-545.
10. Zahavi I, Chagnac A, Hering R, Davidovich S, Kuritzky A. Prevalence of Raynaud's phenomenon in patients with migraine. *Arch Intern Med*. 1984; 144:742-744.
11. O'Keeffe ST, Tsapatsaris NP, Beetham WP Jr. Increased prevalence of migraine and chest pain in patients with primary Raynaud disease. *Ann Intern Med*. 1992;116(12 Pt 1):985-989.
12. O'Keeffe ST, Tsapatsaris NP, Beetham WP Jr. Association between Raynaud's phenomenon and migraine in a random population of hospital employees. *J Rheumatol*. 1993;20:1187-1188.
13. Smyth AE, Hughes AE, Bruce IN, Bell AL. A case-control study of candidate vasoactive mediator genes in primary Raynaud's phenomenon. *Rheumatology (Oxford)*. 1999;38:1094-1098.
14. Voulgari PV, Alamanos Y, Papazisi D, Christou K, Papanikolaou C, Drosos AA. Prevalence of Raynaud's phenomenon in a healthy Greek population. *Ann Rheum Dis*. 2000;59:206-210.
15. Cakir N, Pamuk ON, Dönmez S, et al. Prevalence of Raynaud's phenomenon in healthy Turkish medical students and hospital personnel. *Rheumatol Int*. 2008;29:185-188.
16. Chikura B, Moore T, Manning J, Vail A, Herrick AL. Thumb involvement in Raynaud's phenomenon as an indicator of underlying connective tissue disease. *J Rheumatol*. 2010;37:783-786.
17. Wigly FM. Pathogenesis of the Raynaud phenomenon. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. Available at: https://www.uptodate.com. Accessed February 24, 2019.
18. Bunker CB, Terenghi G, Springall DR, Polak JM, Dowd PM. Deficiency of calcitonin gene-related peptide in Raynaud's phenomenon. *Lancet*. 1990; 336:1530-1533.
19. Khouri C, Blaise S, Carpentier P, Villier C, Cracowski JL, Roustit M. Drug-induced Raynaud's phenomenon: Beyond β-adrenoceptor blockers. *Br J Clin Pharmacol*. 2016;82:6-16.
20. Mohokum M, Hartmann P, Schlattmann P. The association of Raynaud syndrome with β-blockers: A meta-analysis. *Angiology*. 2012;63:535-540.
21. Coffman JD, Rasmussen HM. Effects of beta-adrenoreceptor-blocking drugs in patients with Raynaud's phenomenon. *Circulation*. 1985;72:466-470.
22. Heintzen MP, Strauer BE. Peripheral vascular effects of betablockers. *Eur Heart J*. 1994;15(Suppl. C):2-7.
23. Propranolol: Drug information. Lexicomp. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. Available at: https://www.uptodate.com. Accessed February 24, 2019.
24. Liegl CA, McGrath MA. Ergotism: Case report and review of the literature. *Int J Angiol*. 2016;25:e8-e11.
25. Nagy AJ, Gandhi S, Bhola R, Goadsby PJ. Intravenous dihydroergotamine for inpatient management of refractory primary headaches. *Neurology*. 2011;77:1827-1832.
26. Sumatriptan drug information. Lexicomp. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. Available at: https://www.uptodate.com. Accessed March 24, 2019.
27. Ergotamine: Drug information. Lexicomp. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. Available at: https://www.uptodate.com. Accessed February 24, 2019.
28. Dihydroergotamine: Drug information. Lexicomp. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. Available at: https://www.uptodate.com. Accessed February 24, 2019.
29. Coleiro B, Marshall SE, Denton CP, et al. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford)*. 2001;40:1038-1043.
30. Rudnick A, Modai I, Zelikovski A. Fluoxetine-induced Raynaud's phenomenon. *Biol Psychiatry*. 1997; 41:1218-1221.