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**Echoes of Change: How Ultrasound Has Transformed
Giant Cell Arteritis Detection**

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Echoes of Change: How Ultrasound Has Transformed Giant Cell Arteritis Detection

Maria Powell, MD, MSc (Med Ed), CIP, FRCPC
Mohammad Bardi, MD, FRCPC

Introduction

Giant cell arteritis (GCA) is the most common form of vasculitis affecting adults. The diagnosis of GCA is suspected in patients older than 50 years of age with a new headache and elevated inflammatory markers. Once the diagnosis of GCA is suspected, patients require urgent treatment with glucocorticoids to prevent ischemic complications such as blindness and stroke. As there are many causes for headache, diagnosing GCA can be a 'headache' for many rheumatologists. For years, rheumatologists have relied on the temporal artery biopsy (TAB) as the gold standard for diagnosing GCA, despite the 33–92% sensitivity.¹ As patients with suspected GCA remain on high doses of glucocorticoids, which have multiple side-effects and potential adverse events, rapid access to tests that have a greater impact on clinical decision-making is essential.² Vascular imaging is a non-invasive tool that can help diagnose, monitor, and predict the course of GCA. This article will focus on how ultrasound has transformed the detection of GCA and its potential to reduce some of the 'headaches' faced by both rheumatologists and patients.

Epidemiology

GCA is a large vessel (LV) vasculitis that has a predilection for the temporal artery and its branches but it can also affect the aorta, its branches, and the orbital arteries.³ The incidence of GCA increases with age, and women are more commonly affected by GCA than men, with a ratio of 3:1.^{4,5} Polymyalgia rheumatica (PMR) is a disease that significantly overlaps with GCA; approximately 50% of patients with GCA also have PMR, while approximately 20% of patients with PMR also have GCA.^{6,7}

Pathophysiology

Disease induction and progression of GCA are due to a failure of immune tolerance. Factors including age-related loss of regulatory T-cells and/or genetic deficiencies contribute to unopposed T-cell activation.⁵ Increased endothelial permeability, partly related to aging, allows inflammatory T-cells to enter the otherwise immune-privileged blood vessel wall, triggering a cascade of events that leads to the infiltration of pro-inflammatory mediators. This inflammatory milieu leads to vascular inflammation, which results in changes that can be observed on ultrasound as concentric intima and media thickening, creating a 'halo' around the lumen of the blood vessel.⁸ While ultrasound reliably shows vessel wall edema, it does not provide ultrasonographic features specific for the location of granulomatous inflammation, the presence of giant cells, or regions of disruption of the internal elastic lamina, which explains the limited efficacy of ultrasound for guiding the TAB site in GCA.⁹

Clinical Presentation

GCA is classically recognized in patients presenting with new onset headache, jaw claudication, visual symptoms, scalp tenderness, and temporal artery abnormalities.¹⁰ However, vascular imaging has expanded our understanding of GCA and its clinical manifestations. We now better appreciate that GCA can be stratified into clinical subsets based on the site of inflammation, including cranial GCA, LV-GCA, and LV-GCA with cranial involvement.¹¹ As such, not all patients with GCA present with cranial symptoms; those with LV involvement are more likely to have vascular abnormalities such as bruits, blood pressure asymmetry, abnormal pulses, and/or constitutional symptoms, while

those with overlapping PMR can have pain and stiffness in the shoulder and hip girdles.^{6,11}

Diagnosis

The diagnosis of GCA is clinical, involving a combination of patient history, physical examination, laboratory investigations, and imaging parameters. Traditionally, TAB has been the gold standard for confirming a GCA diagnosis.¹² While TAB can investigate suspected cranial GCA and LV-GCA with cranial involvement, it has several shortcomings, including variable sensitivity (range from 33%–92%), skip lesions, and a focus on cranial GCA.¹³ These drawbacks highlight the appeal of using imaging to guide GCA diagnosis.

Ultrasound assessment of the cranial arteries in GCA involves scanning the common temporal arteries and the frontal and parietal branches. Patients with occipital headaches may benefit from assessing the vertebral and occipital arteries, while those with jaw claudication may benefit from having the maxillary and facial arteries scanned. Ultrasound assessment of the extra-cranial arteries most commonly includes the axillary arteries but can also include the subclavian arteries, parts of the ascending aorta and aortic arch, as well as the femoral and popliteal vessels.¹⁴ A 2023 systematic review and meta-analysis concluded that the pooled sensitivities and specificities for using ultrasound to assess the cranial arteries for the diagnosis of GCA are 88% (95% CI 82%–92%) and 96% (95% CI 86%–99%), respectively.¹⁵ The sensitivity increases to 93% (95% CI 88%–96%) when ultrasound is used to assess both the cranial and extra-cranial arteries, without any loss in specificity.¹⁵ As such, the recommended minimal GCA scan is currently the length of the common superficial temporal arteries bilaterally, the frontal and parietal branches of the superficial temporal arteries bilaterally, and the axillary arteries bilaterally.¹⁶

The intima of normal arteries is very thin. In GCA, concentric intima and media thickening occur due to inflammatory infiltrates and edema in the vessel wall, known as the halo sign.⁸ According to Outcome Measures in Rheumatology (OMERACT), the halo sign is defined as a homogenous, hypoechoic wall swelling visible in both longitudinal and transverse planes (Figure 1c/d/g).¹⁷ The compression sign, also defined by OMERACT, occurs when the thickened arterial wall remains visible upon compression (Figure 1e/f).¹⁷ A non-compressible halo sign

Recommended minimal GCA scan
• Common superficial temporal arteries bilaterally
• Frontal and parietal branches of the superficial temporal arteries bilaterally
• Axillary arteries bilaterally
Technical Requirements:
• High frequency (preferably >18 MHz) linear probe for temporal arteries
• A 7–15 MHz probe for extra-cranial supra-aortic arteries
• Ultrasound machine with both B-mode and colour Doppler and/or power Doppler

Box 1. GCA Scan Requirements; courtesy of Maria Powell, MD, MSc (Med Ed), CIP, FRCPC and Mohammad Bardi, MD, FRCPC.

in the temporal arteries and their branches is highly suggestive of GCA.¹⁸ The intima-media thickness (IMT) can also be measured using ultrasound and compared to standard cut-offs for healthy age-matched controls, with higher IMT being more suggestive of GCA.¹⁹ Recently, the slope sign of the axillary artery has been described as a feature of GCA.²⁰ The slope sign describes a smooth transition from normal to increased IMT in the axillary artery in patients with GCA and can help differentiate vasculitis from other causes of arterial wall thickening, such as atherosclerosis (Figure 1g).²⁰

In 2022, the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) updated the classification criteria for GCA to include the role of ultrasound.²¹ This classification criteria uses a point system that includes ten items, requiring a score of at least six points to classify a patient with GCA. According to these recommendations, a patient with a positive halo sign or a positive TAB, along with features from the history, and/or physical examination, laboratory tests, and/or imaging parameters in various combinations can be classified as having GCA (Table 1). Using these criteria, both TAB and ultrasound evidence of the halo sign are equally weighted (five points), while ultrasound carries the most weight (seven points) due to

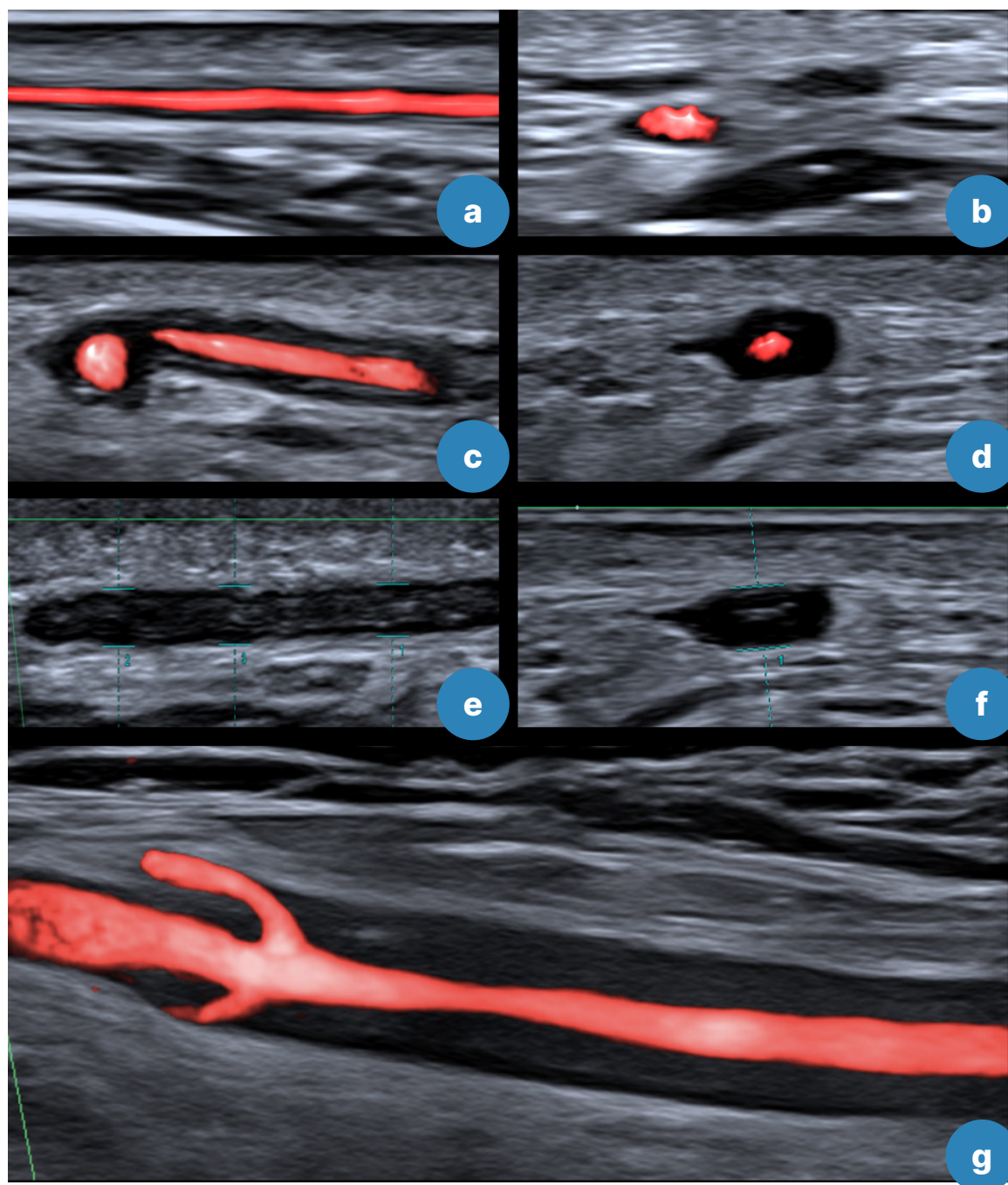


Figure 1. Normal artery in a healthy patient versus abnormal artery in a patient with giant cell arteritis (GCA). Normal common temporal artery in uncompressed longitudinal (a) and transverse (b) views. Abnormal common temporal artery in uncompressed longitudinal (c) and transverse (d) views with evidence of a halo sign (homogenous, hypoechoic wall swelling seen in the image as a dark area around the vessel). Abnormal common temporal artery in compressed longitudinal (e) and transverse (f) views with evidence of compression sign (thickened arterial wall remains visible upon compression). Large vessel vasculitis seen in an axillary artery in longitudinal view with evidence of slope sign (smooth transition from normal to increased intima-media thickness (seen in the image as a dark area around the vessel) (g); courtesy of Maria Powell, MD, MSc (Med Ed), CIP, FRCPC and Mohammad Bardi, MD, FRCPC.

Absolute Requirement	
Age >50 years at the time of diagnosis	
Additional Clinical Criteria	
Morning stiffness in the shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery	+2
Laboratory, Imaging, and Biopsy Criteria	
Maximum ESR >50 mm/hour or maximum CRP >10 mg/liter	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound	+5
Bilateral axillary involvement	+2
FDG-PET activity throughout the aorta	+2

Table 1. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for giant cell arteritis.²¹

Sum the scores for the 10 items, if present.
A score of >6 points is needed for the classification of GCA

Abbreviations: **ESR:** Erythrocyte sedimentation rate, **CRP:** C-reactive protein, **FDG-PET:** Fluorodeoxyglucose-Positron Emission Tomography

the inclusion of LV imaging. While TAB is still preferred by the 2021 ACR/vasculitis foundation guidelines, likely due to GCA ultrasound education being in the early development phases in the United States, the role of ultrasound in the classification of GCA is recognized.

Using ultrasound to diagnose GCA is non-invasive, involves no radiation or contrast, allows for real-time imaging, and can be performed at the bedside. Ultrasound is more sensitive than TAB for GCA diagnosis because it evaluates more than the 1.5 cm of the temporal artery sampled with TAB and can evaluate both the cranial and extra-cranial arteries.¹⁵ Ultrasound assessment of the temporal and axillary arteries is more cost-effective than TAB for diagnosing GCA,

even when accounting for additional factors such as training and equipment.²² Compared to TAB, using ultrasound to diagnose GCA can decrease the length of inpatient admission (from 3.6 days to 0.6 days), reduce steroid comorbidity, and lower the risk of GCA complications such as vision-loss.^{23,24}

Disease Monitoring

Traditional disease monitoring in GCA relies on measuring acute phase reactants such as c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in conjunction with the clinical assessment. However, there are limitations to consider when monitoring laboratory

parameters for GCA. Inflammatory markers can increase for reasons other than disease relapse such as infections, cancer, and other inflammatory disorders, and patients can experience disease relapse with normal inflammatory markers.²⁵ This is further complicated by treatment with interleukin (IL)-6 inhibitors, which make CRP measurements unreliable.²⁶ Additionally, patients with GCA can experience headaches, jaw pain, vision changes, and other symptoms compatible with GCA without a true disease relapse. Ultrasound can assist with disease monitoring in GCA by confirming improvement and/or normalization of wall thickening in involved vascular territories after treatment. On ultrasound assessment, regression of the halo sign of the temporal arteries occurs as early as 48 hours, while regression of the vessel wall edema in the axillary arteries can take several months.²⁷ By using ultrasound to assess the IMT and/or the number of vessel segments with a halo sign compared to the last measured value, rheumatologists can make crucial decisions to escalate or de-escalate immunosuppressive therapy.²⁸ This approach may be particularly valuable when there is discordance between a patient's clinical assessment and laboratory markers.

Prognosis

The ACR/vasculitis foundation recommends obtaining non-invasive vascular imaging for patients newly diagnosed with GCA to help capture the full extent of vascular involvement and predict the disease phenotype (cranial GCA versus LV-GCA versus both).^{11,29} Ultrasound can be used to tabulate a halo score, which includes an assessment of the thickness of the halo sign in eight segments of the temporal and axillary arteries.³⁰ The halo score can help identify a subset of GCA patients with increased intimal hyperplasia who are at a higher risk of ischemic complications such as visual-loss and stroke.^{30,31} The OMERACT GCA Ultrasonography Score (OGUS) includes measurement of the IMT of these same 8 arterial segments, divided by the normal IMT values for each segment, and can be used to predict early relapses during the first 6 months after treatment initiation.^{32,33} Thus, using ultrasound to risk-stratify patients with GCA can be informative for rheumatologists as they counsel patients on treatment options.

Limitations and Considerations

Despite its advantages, there are limitations and considerations when using ultrasound to guide the diagnosis of GCA. First, to accurately use ultrasound to assess for evidence of GCA, a high frequency (preferably >18 MHz) linear probe with a small footprint is recommended for imaging the temporal arteries and a 7–15 MHz probe is recommended for imaging the extra-cranial supra-aortic arteries. The ultrasound machine must be capable of using both B-mode and colour Doppler and/or power Doppler. These machines can be expensive and have limited portability. Second, while select rheumatologists are learning how to perform vascular ultrasound, ultrasound training is not currently a mandatory part of the Canadian rheumatology training objectives (listed as an optional competency).³⁴ Thus, performing vascular ultrasound carries a high upfront cost for interested rheumatologists, who will require the proper equipment and training before using it to guide GCA diagnosis. We as authors prefer that rheumatologists perform the ultrasound assessment, as conducting the imaging separately from the clinical assessment reduces the reliability of the examination and increases the variability of treatment initiation. However, other health professionals, such as radiologists, can participate in the scanning depending on the centre and their expertise.³⁵ Third, although ultrasound is excellent for assessing the cranial and supra-aortic arteries, even when using low-frequency probes, it can currently only reliably assess the first 4 cm of the ascending aorta and aortic arch, and the assessment of the thoracic aorta is limited.¹⁴ As such, other imaging modalities such as [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET), MRI or CT must be used if involvement of these vascular territories is suspected.¹⁶ Fourth, a false positive halo sign can be observed in other conditions such as amyloidosis, lymphoma, infection, and small vessel vasculitis.³⁶ Thus, the sonographer must be trained to differentiate vasculitis from infection, malignancy, and other primary rheumatic disorders. Finally, while ultrasound assessment of the cranial arteries is highly accurate, there is a rapid reduction in accuracy after initiation of glucocorticoids. The cranial arteries remain positive for only 3–7 days, with 50% remaining positive at three weeks.¹⁴ To preserve the accuracy of ultrasound assessments for suspected GCA, the establishment of a GCA ultrasound fast-track clinic is recommended.³⁷

Conclusions

Using ultrasound to guide the diagnosis of GCA is non-invasive, highly accurate, cost-effective, and improves patient outcomes. It has transformed our ability for early detection, disease stratification, and prognostication in GCA, providing rheumatologists with more confidence as they evaluate patients with headaches and suspected LV vasculitis.

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Contemporary Management of Raynaud's Phenomenon

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Raynaud's phenomenon (RP) is defined as reversible pallor, and also rubor or cyanosis especially digits and it is very common on the general population. It can be an early sign of a connective tissue disease, especially scleroderma and may negatively impact patients' quality of life. Lifestyle modifications including smoking cessation, cold-avoidance, and avoidance of medications that could worsen RP should be considered as first-line therapies. For those who are resistant to conservative measures, dihydropyridine calcium channel blockers (CCBs) are the preferred first-line treatment. The majority of treatment trials in RP study nifedipine, but other drugs such as amlodipine and felodipine. Otherwise, there is evidence supporting the use of topical nitrates and oral phosphodiesterase type 5 (PDE5) inhibitors. Intravenous prostaglandins (prostanoids, PGI₂ such as iloprost and PGE₁ which is alprostadil) can be used for refractory cases. There remains a paucity of data for the benefit of botulinum toxin, fluoxetine, or bosentan for treating RP in these patients.

Introduction

Raynaud's phenomenon (RP) is a condition with vasospasm of blood vessels, particularly extremities (especially fingers and toes) where one or more digits have pallor and often rubor and cyanosis. It is common in the general population (approximately 5%).¹ RP can be unrelated to other diseases (primary or idiopathic) or associated with other diseases such as connective tissue diseases (CTDs) and is considered then as secondary RP.¹⁻⁴ RP is caused by small arteriolar vasospasms in digital arteries/arterioles, and is caused by local

interactions between the endothelium, smooth muscle, and autonomic systems.⁵

One of the earliest presenting features of systemic sclerosis (SSc, scleroderma) is frequently RP, and RP may precede other disease manifestations in SSc by several years in the limited cutaneous SSc subset.^{1,2} The pathophysiology of SSc associated RP is poorly understood as often the blood vessels obliterate over time. However, new and emerging treatment methodologies are being explored to help alleviate the symptoms of RP and the associated tissue damage, and these will be discussed in this review.

Lifestyle modifications

For most patients, lifestyle modifications can have a significant impact on moderating the severity of RP. These include smoking cessation, avoiding cold exposure, and using vibration-moderating impact tools for those with occupational exposure. Regarding smoking, both abstinence and cessation are associated with reduced RP symptoms. Patients who smoke heavily are more likely to require admission to the hospital for intravenous vasodilators, while those who have never smoked are 4-fold less likely to require surgical debridement of digital ulcers (a complication of severe RP associated ischemia).⁶⁻⁸ Keeping warm is another key lifestyle modification for those with RP, where cold exposure is a known trigger and is significantly more prevalent in colder climates. There is also seasonal variability; as RP is both more frequent and severe in the colder months.⁹ One study identified that individuals who had frostbite had were 12 times more likely to develop RP.¹⁰ In addition, hand-arm vibration is a known precipitator and exacerbator of RP, with those having occupational risk factors showing a 7-fold higher prevalence of RP.¹¹

Medications can contribute to RP flares and can exacerbate poor peripheral perfusion in these patients. Beta blockers are known to exacerbate RP by increasing alpha-adrenergic tone.¹² One meta-analysis found that the pooled prevalence of RP in those on beta blockers was as high as 14%.¹³ Central nervous system stimulants such as methylphenidate and atomoxetine are associated with RP attacks, cold sensitivity, and even digital autoamputation.¹⁴ Calcitonin gene-related peptide (CGRP) antagonists, an emerging treatment for migraine headaches, have been shown to decrease reflex-vasodilatory responses, and can potentially worsen RP.¹⁵ Some chemotherapies and receptor tyrosine kinases (RTKs) can trigger endothelial dysfunction and increase sympathetic activation, and precipitate RP. Vinblastine, particularly in combination with cisplatin and/or bleomycin, may cause RP.¹⁶⁻¹⁸

For patients who do not respond to the conservative measures mentioned above, pharmacological management is recommended. Interestingly, a meta-analysis of complementary and alternative medicine treatment in RP found that none were more effective compared to placebo.¹⁹

Calcium channel blockers

The European Alliance of Associations for Rheumatology (EULAR) guidelines recommend dihydropyridine CCBs as the first-line treatment for those who fail conservative management described above.^{20,21} Nifedipine was used in the majority of RP data using CCBs. CCBs function in RP by preventing calcium uptake in vascular smooth muscle, which causes vasodilatation, helping to counteract the vasospasm observed in RP.²² A large 2017 Cochrane review of 38 randomized controlled trials (RCTs) investigating CCBs in RP showed a reduction in the frequency of weekly attacks by 6 RP attacks compared to placebo.²³ In addition, CCBs reduced subjective attack severity. Improvement in RP with nifedipine seems dose dependent.²³ A smaller Cochrane review reported a less impressive, but still significant decrease in the frequency of RP attacks in those treated with CCBs compared to placebo.²⁴ Interestingly, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) did not show any benefit in reducing RP severity or the development of digital ulcers compared to placebo.^{25,26}

Nitrates

For patients who can't tolerate CCB treatment, or who prefer a topical route, topical nitrates have been shown effective in treating RP. Topical nitrates function by releasing nitrous oxide within the vascular smooth muscle, activating cGMP-mediated vasodilation.²⁷ A 2018 meta-analysis of RCTs reported a small positive effect of topical nitrates compared to placebo.²⁸ The use of topical nitrates has been shown to improve blood flow to the tips of the fingers, improve finger systolic pressure, and reduce skin discolouration.²⁹ Topical nitrates should be used in low doses to avoid systemic adverse events such as hypotension and headaches.³⁰

PDE5 inhibitors

PDE5 inhibitors are recommended for patients who are non-responsive to CCB treatment for RP or for severe/complicated RP.^{20,21} A meta-analysis suggested a nearly 15 minute reduction in daily RP time with PDE5 treatment.³¹ Another meta-analysis of 9 RCTs of PDE5i in severe RP (mostly secondary to SSc), reduced pain with treatment.³² There is likely a dose range that can improve RP more. The side-effects sometimes limit treatment. For

instance, sildenafil is associated with headaches or facial flushing occur in 10% of patients, and 1 in 50 may experience visual impairment.³³ Patients may become hypotensive especially if used with nitrates.³⁴ Vardenafil and tadalafil have similar side-effect profiles to sildenafil, and should not be taken in combination with nitrates, alpha-adrenergic antagonists, or antiarrhythmics.³⁵⁻³⁸ One RCT investigating sildenafil in RP found a significant improvement in digital ulcer healing with sildenafil compared to no treatment.³⁹

Prostaglandin analogues

Intravenous prostaglandin analogues have been shown to induce peripheral dilation and improve outcomes in patients with RP who were resistant to treatment with conventional therapies. EULAR guidelines only recommend prostaglandin analogues after failure of oral therapies.²¹ Iloprost has positive RCT data and daily treatment for 5 days of peripheral IV therapy yields improvement for several months on average reducing the frequency of attacks.⁴⁰ A RCT on alprostadil showed a 20% reduction in RP events in the first week compared to placebo, along with a reduction in overall severity but the results were not sustained beyond the short term.⁴¹

Fluoxetine

The most recent EULAR guidelines suggest limited evidence for the use of fluoxetine, recommending it if patients are not tolerant to the aforementioned therapies or if those therapies are contraindicated.⁴¹ A small 2001 RCT of 26 patients showed that the mean frequency of RP attacks was 3 in the fluoxetine group compared to 1.5 in the control. There was also a mean reduction in severity by 20%.⁴² However, in general fluoxetine is not used for RP due to weak evidence unless if RP is mild and the patient has another reason to require a selective serotonin reuptake inhibitor (SSRI) such as depression or anxiety.

Ketanserin

Ketanserin, a 5HT_{2A} receptor antagonist with known vasodilatory properties, is thought to improve digital blood flow. It was studied in RP decades ago, and is not used in Canada. While the proportion of patients who improved was higher with ketanserin, it did not show a decrease in the

severity of RP attacks, and its side-effect profile was significantly higher than that of the placebo.⁴³

Botulinum toxin

Until recently, the use of botulinum toxin to treat RP was primarily based on small uncontrolled studies.^{44,45} Botulinum toxin inhibits adrenergic responses and promotes vasodilation. Two small RCTs evaluated the use of botulinum toxin in RP. One trial with 16 patients reported improvements in composite scores, dermoscopic patterns, and nailfold capillary pattern scoring in the botulinum group compared to the control group.⁴⁶ A subsequent larger multicentre RCT did not show any differences in outcomes between the botulinum toxin and controls.⁴⁷ There remains a paucity of evidence for the use of botulinum toxin, and more research is needed in larger cohorts to make definitive treatment conclusions.

Endothelin receptor antagonists (Bosentan and Macitentan)

Bosentan, a dual endothelin receptor antagonist (ERA) used in the treatment of pulmonary arterial hypertension (PAH) and has been studied in RP. Observational studies found reduced severity and frequency of RP attacks,⁴⁸ however, a 2010 RCT found no benefits in patients unless they had pre-existing severe digital ulceration.⁴⁹ Bosentan can reduce the number of new digital ulcers in SSc, but doesn't heal ulcers nor improve RP.^{50,51} EULAR SSc recommendations are for the use of bosentan only for SSc patients with multiple digital ulcers to reduce new ulcers.²¹ Bosentan is not approved in Canada for this indication but is approved in PAH. Macitentan another ETA did not improve digital ulcers in patients with SSc added to background therapy.⁵²

Conclusion

Treatment for RP includes lifestyle modifications, CCBs, and PDE5 inhibitors. For patients who are refractory to first-line treatments, intravenous prostanoids can be used but it is difficult to obtain iloprost in Canada as it is not approved and has no drug information number (DIN) in Canada, so it has to be approved by Health Canada and obtained from another country. Other therapies used in RP trials are in general unhelpful. Fortunately the majority of Canadians who have RP will never need pharmacological therapy.

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The 2023 ACR/EULAR Classification Criteria for Antiphospholipid Syndrome: Implications for the Inclusion of Participants in Research vs Diagnosis in Clinical Practice

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Background

Antiphospholipid syndrome (APS) was first described in patients with systemic lupus erythematosus in 1983,¹ and the primary version in 1989.² Multiple clinical manifestations have been associated with antiphospholipid antibodies (aPL) including venous and arterial

thromboses, transient ischemic attack (TIA), obstetric complications, thrombocytopenia, hemolytic anemia, livedo reticularis, transverse myelitis, cognitive dysfunction, cutaneous ulcers, Libman-Sacks endocarditis, and a peculiar type of nephropathy.³ Antiphospholipid antibodies include lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) IgG and IgM, and

anti-beta-2-glycoprotein antibodies (a β_2 GPI) IgG and IgM. Other antibodies such as anti-prothrombin and anti-prothrombin/phosphatidylserine have been proposed as biomarkers of APS, particularly in cases where the standard antibodies are negative, but they are not officially accepted.

Since 1999, the original Sapporo Criteria⁴ and its revised 2006⁵ version have been used for the classification of patients in research studies and for the diagnosis of patients with APS. Despite the broad spectrum of clinical manifestations and serological markers considered by physicians as part of the APS, the original and revised versions of Sapporo Criteria include only venous, arterial and microvascular thrombotic events and specific obstetric events among the clinical manifestations, and aCL IgG and IgM antibodies, a β_2 GPI-IgG and IgM or lupus anticoagulant as the serological markers. Consequently, APS was diagnosed as obstetric and/or thrombotic syndrome, not considering other non-criteria manifestations associated to aPL antibodies. The major limitation of these criteria is that they do not reflect the systemic nature of APS.

Due to the importance of classification criteria in research, the ACR and EULAR assumed the responsibility of encouraging the development and validation of new and improved classification criteria for various rheumatic diseases, including APS, based on the current standards of measurement.⁶

The 2023 ACR/EULAR Classification Criteria for Antiphospholipid Syndrome

The recently published 2023 ACR/EULAR APS classification criteria aimed to have *high specificity for use in observational studies and trials*.^{7,8} The objective is to restrict the inclusion of research study participants to subjects with selected (not all) clinical manifestations associated solely with the standard aPL antibodies. To make the classification stricter, the new criteria provide different weights to the clinical manifestations and the serology. Even more so, acknowledging that competing factors may be associated with the development of clinical manifestations, the weight of a manifestation varies between patients if the presence of competing factors is different between them. Additionally, if a manifestation can be explained by a concurrent disease, the weight is less, or the manifestation is not scored. Obstetrical manifestations are

strictly defined, and future research studies in this area must include investigators with expertise in applying the various definitions. The laboratory criteria include: **a)** aPL test by coagulation-based functional assay (lupus anticoagulant assay); and **b)** aPL test by solid phase-based assay (anticardiolipin antibody and anti- β_2 -glycoprotein-I antibodies) (**Table 1**).

The new criteria include an entry criterion of at least one positive antiphospholipid (aPL) antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1–7 points each) clustered into 6 clinical domains and two laboratory domains. Patients accumulating at least 3 points each from the clinical and laboratory domains are classified as having APS. The laboratory criteria de-prioritize the IgM isotypes of aCL and a β_2 GPI. As a result, having the IgM isotype only of aCL and/or a β_2 GPI antibodies at either a moderate or high level does not fulfill the laboratory criterion. However, having persistent IgG aCL or a β_2 GPI at a medium (40–79 units) or high level (80 or higher), or persistent LAC, is sufficient to fulfill it. So, the clinician has to identify specifically the isotype and levels of the antibodies reported as well as the dates when the tests were performed as persistence of the antibodies or LAC means at least 2 consecutive results at medium or high levels, at least 12 weeks apart.

In clinical practice, the assessment, diagnosis, and treatment of a patient with APS differ from a research setting. While in research, a patient with non-criteria manifestations associated with aPL antibodies will be excluded to participate in the investigation, when consulting with a treating physician, the same patient will be managed under the diagnosis of APS. Diagnosing APS requires experience and judgement by the clinician, who must continue to weigh clinical manifestations against aPL profiles and other potential risk factors.

Classification and diagnostic criteria typically differ from each other. Classification criteria are developed for research purposes, not for clinical diagnosis. Developing diagnostic criteria is much more challenging than classification criteria due to the variety of clinical manifestations that can be seen among the diversity of patients with the same diagnosis. Developing diagnostic criteria with 95–100% sensitivity is virtually impossible; however, developing classification criteria with

ENTRY CRITERIA

At least one documented clinical criterion listed below (domains 1–6)

plus

A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin, or
anti- β_2 -glycoprotein-I antibodies [IgG or IgM]) within three years of the clinical criterion



If absent, do not attempt to classify as APS; If present, apply additive criteria



Additive clinical and laboratory criteria

Do not count a clinical criterion if there is an equally or more likely explanation than APS
Within each domain, only count the highest weighted criterion towards the total score

Clinical Domains	Criteria	Weight
1. Macrovascular (Venous Thromboembolism [VTE])	• VTE with a high-risk VTE profile ^c	• 1
	• VTE without a high-risk VTE profile ^c	• 3
2. Macrovascular (Arterial Thrombosis [AT])	• AT with a high-risk CVD profile ^c	• 2
	• AT without a high-risk CVD profile ^c	• 4
3. Microvascular	Suspected (one or more of the following): • Livedo racemosa (exam) • Livedoid vasculopathy lesions (exam) • Acute/chronic aPL-nephropathy (exam or lab) • Pulmonary hemorrhage (symptoms and imaging)	• 2
	Established (one or more of the following): • Livedoid vasculopathy (pathology ^d) • Acute/chronic aPL-nephropathy (pathology ^d) • Pulmonary hemorrhage (BAL or pathology ^d) • Myocardial disease (imaging or pathology) • Adrenal hemorrhage (imaging or pathology)	• 5
4. Obstetric	• ≥ 3 consecutive pre-fetal (< 10w) and/or early fetal (10w 0d- 15w 6d) deaths	• 1
	• Fetal death (16w 0d–33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	• 1
	• PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	• 3
	• PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	• 4
5. Cardiac Valve	• Thickening	• 2
	• Vegetation	• 4
6. Hematology	• Thrombocytopenia (lowest 20–130 × 10 ⁹ /L)	• 2
Laboratory Domains	Criteria	Weight
7. aPL test by coagulation-based functional assay (lupus anti-coagulant [LAC] test)	• Positive LAC (single-one time)	• 1
	• Positive LAC (persistent)	• 5
8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β ₂ -glycoprotein-I antibody [aβ ₂ GPI] ELISA persistent)	• Moderate or high positive (IgM) (aCL and/or aβ ₂ GPI)	• 1
	• Moderate or positive (IgG) (aCL and/or aβ ₂ GPI)	• 4
	• High positive (IgG) (aCL or aβ ₂ GPI)	• 5
	• Moderate or positive (IgG) (aCL and aβ ₂ GPI)	• 7

Table 1. 2023 ACR/EULAR APS clinical and laboratory domains, criteria and weightings.^{7,8}

99% specificity, such as with the new APS criteria, is feasible.

It is important to understand the meaning of sensitivity versus specificity. In clinical practice, a diagnostic test or criteria should have high sensitivity because the aim is to identify as many patients as possible with the disease/diagnosis. In research, classification criteria should be highly specific because the aim is to avoid including patients without the disease/diagnosis of interest in an investigation study.

The validation of the new APS criteria showed 99% specificity in two cohorts, while the 2006 Sapporo criteria showed specificity of 91% and 86%, respectively. However, the sensitivity of the 2023 APS criteria was 83% and 84% in the two cohorts, while the 2006 Sapporo Criteria had sensitivity of 100% and 99% in both cohorts. The meaning of these values is that among patients with a clinical diagnosis of APS according to the treating physicians, the new criteria failed to identify 16%–17% of APS patients; however, among those who fulfilled the criteria, only 1% did not have APS.

In the manuscript reviewing the new APS criteria, the authors identified the following false-negative clinical scenarios that failed to meet the APS classification criteria.^{7,8}

1. Patients with an acceptable clinical criterion and moderate- or high-titer IgM aCL/anti- β_2 GPI alone; i.e. a young patient with stroke, or VTE/PE with persistently positive IgM aCL or β_2 GPI only.
2. VTE or arterial thrombosis alone in patients with high-risk profiles for VTE or CVD with an acceptable laboratory criterion; i.e. patient with stroke or VTE/PE with medium-high levels of IgG aCL or β_2 GPI antibodies or LAC with comorbidities such as diabetes, artery hypertension, heavy smoker, dyslipidemia, etc.
3. Occurrence of 3 or more consecutive pre-fetal deaths and/or early fetal deaths, or 1 or more fetal deaths alone in the context of an acceptable laboratory criterion

Other potential false-negative scenarios will continue to be identified.

Due to the lack of a gold standard for diagnosing many rheumatic diseases, clinicians tend to use classification criteria to support the clinical diagnosis. The correlation between classification and diagnosis will be perfect only when the criteria have 100% sensitivity and specificity. It is important for clinicians to understand the limitations of using classification criteria for diagnosis because ultimately, many more physicians caring for patients with APS will read and use the classification criteria than investigators applying the same criteria in clinical studies/trials.

From the clinical perspective, the *2023 ACR/EULAR APS criteria capture the systemic nature of APS* incorporating some of the non-criterion clinical manifestations associated with aPL antibodies including thrombocytopenia, livedoid vasculopathy, nephropathy, valvular disease, pulmonary hemorrhage, and adrenal hemorrhage. As a result, APS will no longer be solely an obstetric and/or thrombotic syndrome.

Conclusion

The 2023 ACR/EULAR APS classification criteria comprise an additive, weighted system, assessing an individual's relative probability of APS and defining a threshold for APS classification for *research purposes*, not diagnosis purposes.

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An Update on the Benefits and Safety Profile of Hydroxychloroquine

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Hydroxychloroquine, an antimalarial drug developed in 1950, has been used for decades in the management of various systemic autoimmune rheumatic diseases. By targeting both the innate and adaptive immune systems, it exerts widespread immunomodulatory effects to attenuate the inflammatory response and exert antirheumatic effects. Its favourable safety profile, coupled with proven benefits in improving disease activity and decreasing morbidity and mortality, especially in patients with systemic lupus erythematosus and rheumatoid arthritis, has solidified its place in the long-term management of patients with rheumatic diseases. Recently, therapeutic drug level monitoring has been used to predict the risks of disease flares and prevent treatment-related toxicity. This review article briefly reviews the benefits of using hydroxychloroquine in the management of systemic autoimmune rheumatic diseases, its common and serious adverse effect profile, and the role of drug blood level monitoring in improving patient-related health outcomes.

Introduction

Hydroxychloroquine, an antimalarial drug that was first synthesized in 1950 and approved by the Food and Drug Administration in 1955, is an immunomodulatory agent that is widely used in Rheumatology to manage a number of systemic autoimmune rheumatic diseases.¹⁻⁸ Hydroxychloroquine is considered the anchor drug in the management of systemic lupus erythematosus (SLE). The European Alliance of Associations for Rheumatology (EULAR)

recommends hydroxychloroquine treatment for all patients with SLE, barring those with contraindications or drug intolerances.² Both the American College of Rheumatology (ACR) and EULAR extend this recommendation further to include pregnant SLE patients, advising that they take hydroxychloroquine during pregnancy considering its benefits for maternal health and in pregnancy.^{3,4} Furthermore, the ACR suggests using hydroxychloroquine, along with Aspirin and heparin, for managing pregnant patients with thrombotic or obstetric antiphospholipid

antibody syndrome (APS).³ In rheumatoid arthritis, hydroxychloroquine can be used as a monotherapy for patients with low disease activity, or, alternatively, as part of combination therapy with other disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine to achieve disease remission.^{5,6} Additionally, hydroxychloroquine has been used as an adjunct therapy for managing patients with obstetric APS who have had recurrent pregnancy losses to improve live birth rates and prevent pregnancy complications.^{3,7-9} Finally, an exploratory clinical trial demonstrated that hydroxychloroquine could reduce the recurrence of congenital heart block (CHB) in a select group of patients with positive anti-SSA antibodies (Ro60 or Ro52 or both) who had had previous pregnancies complicated by CHB.¹⁰ Another trial, the Study of Anti-Malarials in Incomplete Lupus Erythematosus (NCT03030118), is currently underway to evaluate the effects of HCQ on clinical progression of symptoms in patients with incomplete lupus erythematosus, and aims to quantify both patient-reported outcomes and assess changes to their immunologic profile with therapy¹¹. These benefits, coupled with its relative safety and favourable tolerability profile, has solidified the ubiquitous use of hydroxychloroquine in Rheumatology practice.

In this review article, I will briefly summarize hydroxychloroquine's proposed mechanisms of action, discuss its benefits in managing various systemic autoimmune rheumatic diseases, and review its safety profile, including common and serious adverse side effects. I will outline the recent advances in using drug blood level monitoring to improve treatment outcomes and decrease drug-associated toxicity and conclude with a reflection on future directions in the field of hydroxychloroquine research.

Mechanisms of action

Despite decades of use, the precise mechanisms by which hydroxychloroquine modulates the immune response *in vivo* remain largely unclear, with multiple mechanisms hypothesized to play a role in attenuating inflammation. As a weak base, hydroxychloroquine is thought to accumulate in lysosomes, disrupting their participation in cellular autophagy and phagocytosis, thereby impairing lysosome-mediated cellular recycling, the processing of phagocytosed substrates, and antigen processing.^{12,13} This, coupled with

its disruption of toll-like receptor (TLR) 7 and 9 signalling, and cyclic GMP-AMP synthase activation, ultimately interferes with the activation of both innate and adaptive immune systems.^{12,13} It impacts antigen presentation through class II major histocompatibility complexes to effector immune cells, and decreases the downstream production of important cytokines, including interleukin (IL)-1, IL-6, tumour necrosis factor, interferon α and interferon γ .^{12,13} These pleiotropic effects are thought to play a key role in its immunomodulatory and antirheumatic effects.^{12,13}

The Use of Hydroxychloroquine for Managing Systemic Autoimmune Rheumatic Diseases

Hydroxychloroquine is an anchor drug in the management of SLE.² Multiple studies have demonstrated that its sustained use is associated with better health outcomes, including preventing disease flares, decreasing the accrual of disease-mediated organ damage, decreasing the risk of thrombosis, enhancing the cardiovascular risk profile and providing steroid-sparing benefits; it is the only drug used in the treatment of SLE with proven mortality benefit.¹⁴⁻²¹ In a pivotal Canadian clinical trial, withdrawal of hydroxychloroquine therapy in patients with clinically stable SLE was associated with a 2.5 fold increased risk of disease flare, shorter time to disease flare and a 6.1 fold increased risk of severe disease flare necessitating withdrawal from the study.¹⁴ Considering these benefits, it is recommended that all patients with SLE be treated with hydroxychloroquine in the absence of contraindications.² This recommendation includes pregnant patients with SLE, in whom continued treatment with hydroxychloroquine is recommended due to the risk of precipitating disease flares with drug discontinuation.^{2,4,20} In addition, a substantial body of literature that supports its beneficial effects on maternal and fetal outcomes.^{2,4,20}

In rheumatoid arthritis, hydroxychloroquine treatment is indicated for managing patients with mild disease, or as part of a combination strategy with other conventional synthetic DMARDs such as methotrexate and sulfasalazine, to target disease remission and improve clinical outcomes.^{5,6,22,23} In both rheumatoid arthritis and SLE, hydroxychloroquine treatment is associated with improved glycemic control and a decreased risk of incident diabetes mellitus, likely by its role in preventing insulin degradation and improving

peripheral insulin sensitivity.²⁴⁻²⁶ Moreover, hydroxychloroquine treatment improves lipid profiles, with decreases noted in the levels of low-density lipoprotein, triglycerides, and total cholesterol, while increasing high-density lipoprotein levels.^{21,24,27,28} Furthermore, hydroxychloroquine use is associated with a decreased risk of thrombosis in SLE and a reduced risk of cardiovascular disease morbidity and mortality in rheumatoid arthritis.^{21,24,29,30}

An exploratory clinical trial has shown that hydroxychloroquine can reduce the recurrence of CHB by more than 50% in a select group of pregnant patients with positive anti-SSA (Ro60 and Ro52/TRIM) antibodies who had prior pregnancies complicated by CHB.¹⁰ Furthermore, the use of hydroxychloroquine as adjunct therapy for managing pregnant patients with thrombotic or obstetric antiphospholipid antibody syndrome has been suggested, with prior studies demonstrating a net benefit in improving live birth rates and preventing pregnancy complications including preterm delivery, pre-eclampsia and intrauterine growth restriction.^{3,7-9}

Considering its myriad proven benefits in improving disease activity and decreasing patient morbidity and mortality, especially in patients with SLE and rheumatoid arthritis, hydroxychloroquine has solidified its pivotal role in the long-term management of patients with systemic autoimmune rheumatic diseases.

Safety profile and select adverse effects

Treatment with hydroxychloroquine is generally well-tolerated and relatively safe; nonetheless, a multitude of adverse effects have been reported in the literature which may limit its use. (^{12,13,20,21,31,32} and references therein). Reassuringly, most of these side effects are mild and generally resolve with cessation of the drug.^{12,13,21,31} HCQ desensitization protocols have been described in the literature in patients with HCQ-induced rash and hypersensitivity skin reactions with good effect; this can be considered in patients with bothersome cutaneous eruptions to facilitate continued therapy.³²⁻³³ In cases where treatment with HCQ is not tolerated or contraindicated, chloroquine may be used in its stead or alternatively, quinacrine may also be considered for treatment of cutaneous lupus erythematosus.²

In this section, I will discuss some of the common and serious adverse events associated with hydroxychloroquine use.

a) Cutaneous Adverse Effects

Cutaneous adverse effects have been reported to occur in about 10–25% of patients and range from mild maculopapular eruptions, pruritis, urticaria, and drug-induced psoriasis, to more serious drug reactions such as acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms, and Stevens-Johnson syndrome/toxic epidermal necrolysis.^{13,20,21,31,34} In addition, hyperpigmentation of the skin, nails, and the mucosal surfaces has been reported, as has stomatitis and hair changes including hair loss, hyperpigmentation, and bleaching.^{13,20,34} While most resolve with cessation of the drug, more symptomatic and severe cutaneous adverse effects can be treated with topical and/or systemic corticosteroids, desensitization to HCQ, or in case of HCQ-induced hyperpigmentation, use of laser therapy.⁵¹

b) Gastrointestinal Adverse Effects

Gastrointestinal side effects are common, reported in 10–37% of patients treated with hydroxychloroquine, with nausea, vomiting, abdominal pain, and diarrhea frequently reported.^{12,13,21,31} As with cutaneous reactions, these tend to improve with cessation of drug.^{12,13,21,31} Rarely, changes in taste and severe liver toxicity have also been reported.^{13,31,35,36}

c) Drug-Drug Interactions

Treatment with hydroxychloroquine has been associated with QTc prolongation in some studies, thought to be mediated via its blockade of potassium efflux channels, with reported incidence rates of <1% in the literature.^{13,52,53} Concerns about QTc prolongation and the risk of conduction abnormalities and fatal arrhythmias, especially when used in conjunction with other QT-prolonging medications such as antimicrobials, prompted both the Canadian Rheumatology Association and the ACR to publish position statements and white papers on HCQ safety and risk of cardiotoxicity, respectively.^{12,13,31,52,54} Considering the conflicting data in the literature on the effect of treatment with HCQ on cardiac conduction, there remains uncertainty about whether routine monitoring for QTc prolongation is warranted in patients treated

with HCQ but clinicians may elect to obtain a routine baseline electrocardiogram (ECG) prior to initiation of therapy.^{31,52,54} Moreover, care must be taken when prescribing hydroxychloroquine in combination with other drugs that are also metabolized by cytochromes P450 and 3A4, because these interactions can alter *in vivo* drug levels and lead to treatment-related toxicity and morbidity.^{12,13,31}

d) Cardiac Adverse Effects

While rare, more serious cardiotoxic adverse effects, including cardiomyopathy and conduction system abnormalities, ranging from QTc prolongation to complete atrioventricular block and Torsades de Pointes have been reported with hydroxychloroquine use, especially with higher doses and long-term treatment duration.^{12,13,20,21,31,37} The prevalence of HCQ-related cardiomyopathy and arrhythmias in patients is estimated to be about 3%, as reported in a pharmacovigilance database, with a higher incidence of conduction system abnormalities, of about 15.7%, noted on ECG of patients with SLE treated with HCQ from the Toronto Lupus Cohort.^{12,13,20,21,31,37,52,53} HCQ can result in restrictive, dilated, or hypertrophic cardiomyopathy, and patients may present with signs and symptoms of congestive heart failure or syncope/presyncope, with endomyocardial biopsy showing classic findings of curvilinear bodies, vacuoles, and lysosomal bodies.^{41,52} While conduction abnormalities are generally permanent, cardiomyopathy may improve with drug cessation, with a case series from the Toronto Lupus Clinic describing regression of hypertrophy and improvement in cardiac biomarkers with drug cessation.^{31,37,52}

e) Ocular Adverse effects

The most feared complication with hydroxychloroquine use is ocular toxicity, specifically, retinopathy.^{12,13,20,21,31,38} Ocular adverse effects range from reversible corneal deposits and paracentral scotoma to loss of visual acuity, of night vision, and of peripheral vision in advanced cases.^{13,20,21,31,38}

Prevalence of retinopathy amongst patients treated with HCQ has been reported to be anywhere between 4 and 13% in the literature, with an estimated risk of retinopathy <1% of patients in the first 5 years of therapy, <2% of patients in the first 10 years, ~12% and up to 20% of patients after 20 years of therapy.^{38,39,41,55} Risk factors for development of retinopathy include treatment with doses of hydroxychloroquine that exceed 5 mg/kg of actual body weight, concomitant chronic kidney disease or tamoxifen use, prolonged duration of therapy, high cumulative dose, older age, patients from the sub-Saharan African and West Indies regions, and patients with pre-existing retinal disease.^{12,13,20,21,31,38-40} Recently, a study by Petri *et al.* showed that higher hydroxychloroquine blood levels were also associated with the development of later retinal toxicity, although a smaller study published around the same time did not confirm this association.^{39,40}

Ocular toxicity may be reversible if HCQ is stopped when early signs of toxicity are detected during routine screening examinations.^{13,38,41} However, HCQ-related retinopathy is thought to be irreversible, and can even progress after the drug is discontinued, making early detection crucial to prevent permanent visual loss.^{13,38,41} Considering its significant morbidity and risk of patient harm, the American Academy of Ophthalmology recommends baseline screening retinal examinations to assess for pre-existing macular disease. For patients without major risk factors for the development of retinopathy, annual screening eye exams, including automated visual fields and optical coherence tomography, are recommended after 5 years of therapy.³⁸ Patients with major risk factors for retinopathy should receive individualized screening regimens.³⁸

f) Rare Adverse Effects

A number of other adverse effects have been reported in the literature. These include neurologic adverse events such as headache, reported in about 10% of patients, and tinnitus, dizziness, ataxia, and seizures, all of which are less common and reported in <1%.^{13,41} Neuropsychiatric effects including depressive mood, anxiety, irritability, hallucination, mania, psychosis, and suicidality have been reported with HCQ use but are thought to be generally mild, self-limited, and rare with estimated prevalence rates of 1–5% in one systematic review.^{13,31,41,42}

Finally, myotoxicity has been reported in the literature.^{21,31,41,43} This is usually signalled by elevated muscle enzymes and skeletal muscle weakness, with muscle biopsy demonstrating evidence of vacuoles and curvilinear and lamellar bodies, which typically improves with discontinuation of hydroxychloroquine.^{21,31,41,43}

The Role of Hydroxychloroquine Blood Drug Level Monitoring

Hydroxychloroquine drug levels can be measured in either patient serum or whole blood using liquid chromatography, mass spectrometry, or both.⁴⁴⁻⁴⁶ For the last two decades, hydroxychloroquine drug level monitoring has been used to establish therapy non-adherence and its negative consequences, such as increases in disease activity and flare rates. On the one hand, multiple studies have validated this approach, and have also established the protective effects of therapeutic, stable hydroxychloroquine blood levels (defined in one study to be 750–1200 ng/mL) against disease flares and acute healthcare utilization.⁴⁴⁻⁴⁷ On the other hand, severely subtherapeutic levels, signalling likely therapy non-adherence, were associated with an increased risk of disease flares, accrual of early damage, and mortality.^{44,48} Conversely, supratherapeutic drug levels may be associated with hydroxychloroquine-related toxicity, such as gastrointestinal side effects and skin hyperpigmentation, or signal the development of later drug-related toxicity, such as retinopathy.^{39,49,50}

While hydroxychloroquine drug level monitoring has been in use for almost two decades, it is still not widely used in clinical practice, perhaps due to a perceived lack of access, although it is listed as an available send-out test through a national medical laboratory (DynaCare) as well as through LabCorp and through specialized research laboratories.^{30,39,45,46,47,56,57} The lack of equitable access and difficulties with scalability and reliable blood sampling has impeded its widespread use in clinical practice and clinical guidelines have not outlined recommendations for its use in routine practice apart from recommending that HCQ drug levels be used to guide drug dose adjustments and assess for treatment adherence.² Clinically, it may prove useful to measure HCQ drug levels periodically, for instance, within several months of treatment initiation or modification

to assure treatment adherence and assess for supratherapeutic drug levels, allowing for tailored drug dosing for individual patients. Additionally, it may be worthwhile to check drug levels during disease flares or in patients with persistent disease activity, to assess for treatment non-adherence and allow for targeted patient-centered interventions to improve treatment uptake. Indeed, patients may be more motivated to maintain treatment with HCQ if drug levels were routinely monitored, improving their disease activity and overall trajectory. I suspect that we will be routinely measuring hydroxychloroquine levels as part of clinical care within the next several years.

Conclusions and Future Directions

In summary, hydroxychloroquine has been effectively used for the last several decades for managing a number of systemic autoimmune rheumatic diseases with proven benefits in improving disease activity, decreasing the risks of disease flares and development of damage, and improving clinical outcomes and survival. In addition to its antirheumatic and immunomodulatory effects, hydroxychloroquine has also been shown to modulate glycemic control and lipid metabolism, thereby improving cardiovascular risk profiles in patients with rheumatic diseases and further decreasing their associated morbidity and mortality. It is a generally well-tolerated medication with a largely favourable side effect profile. Although the risk of retinal toxicity increases with prolonged use and higher cumulative doses, established screening guidelines to routinely monitor patients for the development of retinal toxicity can help detect early changes before irreversible damage occurs. In addition, more widespread use of hydroxychloroquine drug level monitoring may help identify patients who are at an increased risk of developing drug-related toxicities in the future prior to the accrual of treatment-related damage.

While significant strides in research have been made to date, including in the last year, I propose that future research efforts can address several unmet needs. Historically, prior studies with higher doses of hydroxychloroquine were used for inducing and maintaining disease remission. However, subsequent to the publication of the American Academy of Ophthalmology 2016 guidelines on hydroxychloroquine-related ocular toxicity, treatment recommendations

have evolved to recommend that doses should not exceed 5 mg/kg of actual body weight.^{2,38} It remains unclear whether these reduced doses are sufficient to induce long-term disease remission, reduce the risk of disease flares, and prevent the accrual of disease-related damage and associated morbidity and mortality. Moreover, considering the increased risk of retinal toxicity in patients with chronic kidney disease, it is unclear whether these patients may require further dose adjustments to prevent drug accumulation and reduce the risk of drug-mediated toxicity. Furthermore, despite decades of experience with this drug, the exact mechanisms by which it exerts its antirheumatic and immunomodulatory effects remains unknown. Further research efforts may help identify new drug targets that similarly modulate the immune response without resulting in significant immunosuppression. Finally, with the advent in the use of hydroxychloroquine blood drug levels, and their association with disease activity and flare rates, there is a need to scale up measurement techniques. This would allow for their widespread adoption and incorporation into routine clinical practice, to improve treatment adherence, decrease the risks of drug-related toxicity, and improve patient-related health outcomes.

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