Candidate drug replacements for quinacrine in cutaneous lupus erythematosus

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ABSTRACT
Cutaneous lupus erythematosus (CLE) is a disfiguring and potentially disabling disease that causes significant morbidity in patients. Antimalarials are an important class of medication used to treat this disease and have been the first-line systemic therapy since the 1950s. Quinacrine, in particular, is used as an adjuvant therapy to other antimalarials for improved control of CLE. Quinacrine is currently unavailable in the USA, which has taken away an important component of the treatment regimen of patients with CLE. This paper reviews the evidence of available local and systemic therapies in order to assist providers in choosing alternative treatments for patients who previously benefited from quinacrine therapy.

INTRODUCTION
Cutaneous lupus erythematosus (CLE) is an autoimmune skin disease that can present as an isolated condition or as part of SLE. CLE lesions can be disfiguring and painful, and can cause psychological and physical distress for patients with CLE.1 The first modern CLE treatments were antimalarials. Originally used for malaria prophylaxis, physicians noted their anti-inflammatory properties in the 1950s and began using hydroxychloroquine, chloroquine and quinacrine for treating a myriad of autoimmune conditions, including CLE. Quinacrine has been most often used as adjuvant therapy for patients with CLE with insufficient response to hydroxychloroquine or chloroquine (mepacrine is a synonymous designation for quinacrine). Quinacrine is favoured as an adjuvant therapy as it does not cause increased risk of retinopathy and requires minimal monitoring.2 It has shown to be effective in treating CLE.3 4 Quinacrine suppresses proinflammatory cytokines tumour necrosis factor alpha and interferon alpha from monocytes and myeloid dendritic cells, and might act on toll-like receptors in a manner that is different from other antimalarials.5 6 Thus, in addition to additive effects, quinacrine might provide synergistic effects to hydroxychloroquine and chloroquine in the treatment of CLE. Previous in vitro studies had suggested that the combination of quinacrine with either hydroxychloroquine or chloroquine might provide synergistic anti-inflammatory benefit.7

However, over the past 30 years, quinacrine availability in the USA has become increasingly scarce. Prior to 1993, quinacrine was manufactured in tablets by Sanofi Winthrop Pharmaceuticals and marketed in the USA under the brand name Atabrine. As Sanofi Winthrop stopped production in the USA, compounding pharmacies took over in obtaining quinacrine from India and compounding it. This system lasted until 2019, when the US Food and Drug Administration (FDA) placed an import alert on Vipor Chemicals, an international manufacturer of quinacrine, based on the Drug Quality and Security Act of 2013.8 9 Vipor Chemicals was the sole manufacturer to have FDA approval for importing quinacrine into the USA prior to 2019.

Unless the original manufacturer undergoes reinspection and approval or other manufacturers are willing to meet the FDA regulatory hurdles, quinacrine will be eliminated as a potential treatment option in the USA. As the availability of quinacrine wanes, it is imperative that dermatologists and rheumatologists reassess their arsenal of therapies, both established and emerging, to adequately treat CLE. Whether it is optimising local versus systemic therapies, finding alternatives to quinacrine will be an ongoing yet crucial process. In this review, the reader will be provided a number of such alternatives based on the published literature, extrapolations from that literature and the combined subspecialty practice experience of the authors.

Maximise photoprotection while maintaining normal vitamin D blood levels
CLE lesions can be aggravated by the sun, and patients with CLE can also experience systemic
symptoms such as fatigue and arthralgias from extended sun exposure. Photosensitivity rates range depending on CLE subtype, with 27%-100% of patients with subacute cutaneous lupus erythematosus (SCLE), 25%-90% of patients with discoid lupus erythematosus (DLE) and 43%-71% of patients with tumid lupus reporting photosensitivity. Therefore, sun avoidance and protection are paramount and should be a fundamental component of the treatment plan. Sunscreens should be broad spectrum with ultraviolet A (UVA) photoprotection and should have a sun protection factor (SPF) 70 or greater due to photosensitivity that accompanies CLE. In Garza-Mayer et al’s study, SPF 60 or greater prevented photoprovocation of discoid lesions in 96% and pigment changes in 51% of patients with CLE.

Sun-protective clothing that blocks ultraviolet (UV) rays can be helpful, depending on the season and photosensitivity of patients with CLE. Clothing items such as rash guard swimwear or solar sleeves offer protection of the arms and minimise UV ray exposure. Consumer products, such as SunGuard Laundry Aid, can add SPF to a patient’s own clothing. In a survey of 28,588 respondents, those who engaged in using sunscreen, seeking shade, wearing a hat and wearing protective clothing had the lowest likelihood of sunburn (6.6%) versus those who only used sunscreen (62.4%). Therefore, a multimodal response encompassing all UV avoidance strategies may be more effective than just sunscreen alone.

Another photoprotection modality is the fern extract Polypodium leucotomos. Its photoprotective properties derive from the phenolic compounds caffeic acid and ferulic acid. P. leucotomos is ingested orally, and these antioxidant compounds counteract UV immunosuppression on dendritic cells and lymphocytes. P. leucotomos supplementation was shown to improve photodermatoses. Caccialanza et al studied the efficacy of P. leucotomos treating polymorphous light eruption (PME), and 29.8% of patients with PMLE normalised, with 43.8% showing some degree of improvement. A similar study by Tanew et al demonstrated that 35 patients with PMLE treated with 2 weeks of P. leucotomos had reductions in UV-provoked lesions, improvement in threshold for UV lesion induction and increased number of UVA exposures to induce lesions. The literature for the role of P. leucotomos in CLE is minimal, with a single case report describing improvement of SCLE with hydroxychloroquine and adjuvant P. leucotomos. While CLE-specific data is scarce, P. leucotomos has an excellent safety profile, is widely available in the consumer market and should be considered as an adjuvant photoprotection treatment.

Maximising the clinical benefit of oral hydroxychloroquine/ chloroquine

While the efficacy of hydroxychloroquine as a CLE treatment has been validated by randomised clinical trials, there are options to further maximise the efficacy of available antimalarials. Among other deleterious health effects, smokers have more refractory disease that is unresponsive to hydroxychloroquine, so smoking cessation is essential. Furthermore, smoking has been associated with an increased burden of CLE lesions irrespective of antimalarial treatment. Pette et al have shown that current smokers with CLE have higher median Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and Skindex 29+3 scores compared with never and past smokers with CLE. Therefore, smoking cessation can potentially improve CLE, in addition to optimising hydroxychloroquine efficacy.

Medication compliance must also be taken into consideration before deciding that a patient is refractory to antimalarial treatment. In a multicentre study regarding hydroxychloroquine compliance, 25% of French patients with SLE were non-compliant based on drug blood levels.

Side effects to hydroxychloroquine can include nausea, which may present as an obstacle in patient compliance. Best practices to optimise hydroxychloroquine compliance can include taking the full daily dose of hydroxychloroquine only once per day rather than split daily doses, taking it nightly to avoid gastrointestinal upset, or beginning with a smaller dose and titrating up. Furthermore, hydroxychloroquine levels can be tested to ensure that a therapeutic blood level range (500–2000 μg/mL) has been reached, usually within several months. If compliance is achieved, yet CLE is not controlled, chloroquine monotherapy can be trialled. Chasset et al found that if an antimalarial agent is discontinued due to adverse effects, it is worthwhile to trial a second antimalarial, as more than two-thirds show good tolerance and sustained improvement to the second agent.

Although chloroquine has a higher risk of retinopathy compared with hydroxychloroquine, it has been observed that chloroquine monotherapy may be more effective in some patients with CLE compared with hydroxychloroquine therapy. Recommendations for maximising the benefits of antimalarial treatment are included in table 1.

Long-term therapy with hydroxychloroquine or chloroquine carries the risk of developing a ‘bull’s-eye’ macular retinopathy. When these drugs began to be widely used to treat autoimmune diseases, including rheumatoid arthritis and SLE in the 1950s and 1960s at very high daily doses (eg, 1000–1200 mg/day), some patients suffered loss of vision. It was subsequently learnt that daily doses of hydroxychloroquine no higher than 6.5 mg/kg/day based on ideal body weight greatly decreased the risk of antimalarial retinopathy (4 mg/kg/day for chloroquine). These daily dose regimens were used successfully over the next several decades in treating CLE and in mitigating the systemic manifestations of SLE, as well as its comorbidities such as premature atherosclerotic cardiovascular disease.

However, in 2016, the American Academy of Ophthalmology published new recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Because of concern about increasing incidence of antimalarial retinopathy, these revised guidelines recommended...
that patients should not receive more than 5 mg/kg/day of hydroxychloroquine based on real body weight (2.3 mg/kg/day for chloroquine). Some rheumatologists and dermatologists have expressed concern that the lower daily doses of hydroxychloroquine and chloroquine resulting from these new screening guidelines could result in breakthrough of CLE and SLE disease activities. Increasing the hydroxychloroquine dose for previously hydroxychloroquine-refractory patients with CLE can significantly improve CLE lesions.\textsuperscript{31} Therefore, doses of antimalarials should be based on the risk:beneft ratio, although HCQ blood levels may be helpful, and in general, it is best to stay within the dosing guidelines because of eye toxicity.

Patients with SLE are often treated with hydroxychloroquine in an uninterrupted fashion long-term in part to mitigate the life-threatening comorbidities of SLE. However, in patients with CLE who respond to hydroxychloroquine, it is sometimes withdrawn after 6–12 months of therapy to be restarted at the time of the next flare of skin disease activity. In this setting, the time periods between episodes of skin disease activity can be months to years. Thus, patients with CLE typically may have lower total cumulative doses of hydroxychloroquine compared with patients with SLE over the same time frame, thus mitigating the risk of antimalarial retinopathy.\textsuperscript{32} Thus, it might be argued that in patients with CLE whose skin disease activity has not responded after an appropriate period of time to hydroxychloroquine 5 mg/kg/day, it may be appropriate to increase the daily dose to 6.5 mg/kg/day, especially if HCQ blood levels are low.

**Local therapy**

Pimecrolimus cream is an immunosuppressive medication that works by inhibiting T-cell activation via the calcineurin pathway. It does not carry the risks of skin atrophy or hypothalamic-pituitary axis suppression like topical glucocorticoids. Its efficacy was first shown in case series which suggested it as an effective alternative to topical glucocorticoids.\textsuperscript{33,34} Its role in CLE was further confirmed in a randomised double-blind clinical trial comparing it to topical glucocorticoids (betamethasone 17-valerate 0.1% cream). Both treatment arms showed significant improvement, suggesting pimecrolimus cream is a safe and effective alternative to topical glucocorticoids.\textsuperscript{35}

Topical tacrolimus also exists as a safe alternative to topical glucocorticoids. One randomised double-blinded trial showed significant improvement using tacrolimus 0.1% ointment compared with placebo in CLE at both 4 and 8 weeks. Though there was no significance compared with placebo at 12 weeks, this may have been due to the small sample size of 30 patients.\textsuperscript{36} Tacrolimus functions through a similar pathway to pimecrolimus and, since it exists in an ointment rather than a cream, may be preferred by some patients. Alternative formulations have been suggested, including a case series using tacrolimus 0.3% lotion. While this limited study of three patients supported the use of tacrolimus 0.3% lotion in CLE, larger prospective studies, as well as improved availability, are needed before this can be considered a reasonable treatment option.\textsuperscript{37} A topical formulation of tacrolimus 0.3% in clobetasol propionate 0.05% ointment in a cohort study of 13 patients with refractory CLE was reported to be more beneficial in CLE than either tacrolimus 0.1% ointment or clobetasol propionate 0.05% ointment alone.\textsuperscript{38}

Topical glucocorticoids have long been a first-line localised therapy for CLE. Unfortunately, chronic use of this class of medication results in well-described side effects, including skin atrophy and telangiectasias. For this reason, pulse topical glucocorticoids are often recommended. This consists of 2 weeks of daily high-potency topical glucocorticoids followed by 2 weeks of topical steroid-sparing agents (such as pimecrolimus/tacrolimus listed previously). This cycle is repeated as long as treatment is required, allowing for the safe use of topical glucocorticoids, even in sensitive or thin-skinned areas.\textsuperscript{39}

**Systemic therapy**

**Anti-inflammatory monotherapy**

Synthetic retinoids have been reported to provide some clinical benefits for CLE. Isotretinoin (Accutane) was the first orally administered synthetic retinoid reported to be of value in CLE.\textsuperscript{40} Acitretin has also been reported to be of value in CLE.\textsuperscript{41} However, the clinical benefit of both oral retinoids appears to be anti-inflammatory rather than remission-inducing as CLE has typically flared soon after these drugs have been discontinued. Furthermore, long-term systemic retinoid therapy carries substantial risk for adverse effects. In addition, CLE often occurs in women of childbearing potential. As both isotretinoin and acitretin carry a high risk of teratogenicity, great caution has to be used in this clinical setting.

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\textsuperscript{3}Evidence levels adapted from the Oxford Centre for Evidence-Based Medicine.

CLE, cutaneous lupus erythematosus; GI, gastrointestinal; HCQ, hydroxychloroquine; SPF, sun protection factor; UV, ultraviolet.
Dapsone has both antibacterial and anti-inflammatory properties and has found success in treating multiple dermatological conditions through the latter. Previous studies showed the response rate for patients with CLE receiving dapsone to be around 50%; however, many of these studies were retrospective and included qualitative measures of cutaneous improvement.42–44 This response rate is similar to that of hydroxychloroquine, the current first-line treatment of choice in the USA.29 In addition, these studies showed dapsone to be well tolerated in patients with CLE. Klebes et al reported that out of 17 patients treated with dapsone, 1 developed a drug reaction with cosinophilia and systemic symptoms; 1 developed peripheral neuropathy that resolved on discontinuation of the drug; and 1 developed haemolytic anaemia.44 Haemolytic anaemia in particular is well described with dapsone use, though rarely clinically significant. Another adverse effect to be aware of with dapsone use is methaemoglobinemia, which is rarely clinically significant but may result in decreased blood oxygenation values on pulse oximetry. Current monitoring recommendations include a complete blood cell count with differential every 2 weeks for 3–6 months, then spaced out to every 2 months. Due to the risk of haemolytic anaemia, dapsone is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.45 In the absence of antimalarials, or in non-responders to these medications, dapsone may be a valid treatment option for CLE.

Thalidomide has shown excellent results in the treatment of CLE based on multiple case series. Its use is limited by the medication’s teratogenicity, as well as its propensity for inducing peripheral neuropathy in patients.46 Thalidomide also carries the risk of thromboembolism, and for this reason, low-dose aspirin is prescribed in addition, though there is no definitive evidence that this prevents thromboembolism in patients with CLE on thalidomide.47 In recent years, lenalidomide, an analogue of thalidomide, has shown efficacy in the treatment of CLE as well. This medication has a much lower risk of side effects, including peripheral neuropathy, but does still carry the risk of teratogenicity and thromboembolism. Although most studies surrounding lenalidomide have been small, the current evidence supports the use of lenalidomide, especially in difficult cases of refractory CLE.48–51

Sulfasalazine is a medication used in multiple inflammatory disorders, including rheumatoid arthritis and Crohn’s disease, though rarely used in dermatology outside of psoriasis. Its exact mechanism is unclear, though it does appear to have both immunosuppressive and anti-inflammatory effects. Previous studies have shown that it decreases levels of both CD4 helper T cells, as well as arachidonic acid metabolites in the dermis.52 An open-label study of 13 patients on sulfasalazine monotherapy for DLE showed what the author considered an excellent response rate in 6 patients and at least moderate response in 9 patients.53 Another open-label study the following year showed a complete response in 7 out of 11 patients.54 While there have been limited publications on the use of sulfasalazine in CLE, this represents a safe and inexpensive option with efficacy similar to other more well-described treatments.

Combination therapy with hydroxychloroquine

As the available medications for CLE have variable efficacy, combination therapy is frequently required for disease control. The efficacy and safety of triple therapy, including hydroxychloroquine, methotrexate and sulfasalazine, are well studied in rheumatoid arthritis.55 56 While such efficacy for rheumatoid arthritis does not necessarily translate to CLE, it is well known that these drugs have some beneficial effect in CLE. This supports the idea that medications may be combined with methotrexate to further improve active CLE with a low risk of increased toxicity. Hydroxychloroquine and dapsone have been used in combination with success in other autoimmune inflammatory conditions such as rheumatoid arthritis.57 The combination of hydroxychloroquine and dapsone has been used successfully and safely in patients with vesiculobullous SCLE.58 Thus, consideration could be given to adding dapsone to hydroxychloroquine in other clinical forms of CLE. However, dapsone should be avoided in individuals who have glucose-6-phosphate dehydrogenase deficiency.59

Small molecule immunosuppressive/immunomodulatory

Methotrexate monotherapy has been used to successfully treat SLE for decades, and more recently to treat CLE if first-line antimalarials are inadequate. It is more tolerable than other immunosuppressant medications available and at the doses used for CLE has a more favourable side effect profile. There have been several case series supporting its use and reporting mostly mild side effects, though patients must be monitored with long-term use of the medication due to the risk of myelosuppression.59–62 In addition, methotrexate should be avoided in patients who drink alcohol, have fatty liver, have decreased renal function or have underlying liver disease.63 Oral methotrexate intolerance can be mitigated by switching to subcutaneous injection. In addition, subcutaneous methotrexate can be used in higher weekly doses than oral methotrexate.

Mycophenolate mofetil is an immunosuppressive medication initially used in transplant patients that has been subsequently used in SLE, specifically for lupus nephritis.64 Following its success with SLE, it was tried in CLE-specific disease, proving efficacious in treating the various subtypes of CLE.65 66 The medication is typically well tolerated, with gastrointestinal disturbance being the primary side effect in patients.67 This side effect can be avoided by using an enteric-coated formulation, or using mycophenolic acid rather than mycophenolate mofetil.66 The decision to use methotrexate or mycophenolate mofetil as the first-line immunosuppressant in patients with CLE should be based on the medication’s tolerability and any comorbidities the patient has that would favour one medication over the other.
Azathioprine is a derivative of 6-mercaptopurine that has anti-inflammatory and immunosuppressive effects. The evidence for azathioprine in CLE is based mostly on case reports and retrospective studies. For these reasons, azathioprine is not routinely recommended for use in CLE unless other treatment options have been exhausted.

Leflunomide is an isoxazole derivative that primarily acts through inhibiting dihydroorotate dehydrogenase, an enzyme involved in pyrimidine synthesis, which is critical for the clonal expansion of lymphocytes. It has been well studied in SLE and appears to be an effective and safe therapeutic option, especially for arthritis. It has shown a wide spectrum of effects in CLE, including both remission and deterioration of disease. In addition, there are multiple reports of drug-induced SCLE in patients with no history of CLE. No prospective studies using leflunomide for CLE have been published, and the current literature paints an unclear picture of its role in this disease.

The overproduction of type I interferon that occurs in CLE lesions is transduced into proinflammatory cytokine production via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) intracellular signalling pathway. Recent work has revealed that, in addition to its other mechanisms of action, methotrexate inhibits the proinflammatory JAK/STAT signalling pathway. Moreover, as leflunomide is also a JAK/STAT pathway inhibitor, it has been suggested these two drugs used together might have additive or synergistic JAK/STAT pathway-inhibiting activities. However, it should be noted that the authors have no personal experience in using this drug combination in CLE.

Targeted therapies

Belimumab is a monoclonal antibody that inhibits B-lymphocyte stimulator (BLYS) and was FDA approved for use in SLE in 2011. BLYS is involved in promoting B-cell survival, and its inhibition causes apoptosis of the autoreactive B cells active in SLE. While multiple clinical trials have shown it to be effective in SLE, its role in CLE is less clear. These trials specifically enrolled SLE patients, and while some did have skin disease, there was no strong focus on skin-specific lupus erythematosus. A label study of five patients with CLE showed a good clinical response based on CLASI scores; however, larger prospective studies are needed to truly determine its role in CLE.

Rituximab has mixed reports in its utility for lupus erythematosus. Rituximab is used in SLE based on the efficacy seen in retrospective study data, though subsequent clinical trials have not confirmed these findings. A prospective study by Vital et al showed a 43% response rate in acute CLE and no response in chronic CLE, including DLE. In addition, some patients with chronic CLE had worsening disease with new lesions appearing following rituximab therapy. Another retrospective study showed greater efficacy for rituximab among acute CLE and non-specific cutaneous lesions in SLE. Based on this information rituximab may be a reasonable choice in acute CLE or non-specific cutaneous lesions in SLE, and should be avoided in subacute and chronic CLE.

Intravenous immunoglobulin (IVIG) has been used successfully to treat autoimmune diseases and in rare cases has been used to treat CLE. There are mixed results regarding the use of IVIG in CLE, including a case series of seven patients by De Pità et al showing no improvement in cutaneous disease. Following this study, there have been multiple case reports supporting the use of IVIG in refractory CLE with improvement in cutaneous lesions and minimal side effects. An open-label study consisting of 12 patients described complete or near-complete improvement of cutaneous disease in 75% of patients with limited side effects. While there may indeed be some benefit to IVIG use in patients with CLE, the high cost and limited number of studies make this a less supported treatment better reserved for refractory CLE that has failed other more common treatments. A summarised list of the available recommended systemic drugs for CLE is shown in table 2.

New medications are also being developed to target type I interferon, an important driver of CLE pathogenesis. BIIB059 is a humanised IgG1 monoclonal antibody that targets blood dendritic cell antigen 2. This protein is uniquely expressed on plasmacytoid dendritic cells, a main component of the type I interferon pathway active in CLE. BIIB059 binds to this protein, inhibiting type I interferon production and decreasing the number of plasmacytoid dendritic cells. In a phase Ib study, significant improvement was shown in cutaneous disease based on CLASI scores, and the drug was well tolerated.

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<th>Table 2</th>
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<td>Azathioprine</td>
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<td>Belimumab</td>
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*Evidence levels adapted from the Oxford Centre for Evidence-Based Medicine. IVIG, intravenous immunoglobulin.*
addition, a phase II study for the same medication study met primary end points in SLE and CLE compared with placebo, and further strengthened the safety data available for the drug. Anifrolumab is a human IgG1κ monoclonal antibody that targets the same pathway by binding to type I interferon receptor and blocking type I interferon signalling. This molecule recently completed a successful phase III clinical trial for SLE and was also shown to be superior to placebo in reducing skin disease activity.

In addition to these monoclonal antibodies, new immunomodulatory molecules are also being developed. Iberdomide is a derivative of lenalidomide and functions as a cereblon modulator, with higher affinity for cereblon than lenalidomide. Through binding cereblon, it is able to degrade the transcription factors Ikaros and Aiolos, leading to downstream antiproliferative and immunomodulatory effects that are therapeutic in SLE. It showed efficacy in a recent phase II dose escalation study, meeting endpoints for the treatment of both SLE and CLE. The therapies currently under development for use in CLE are summarised in table 3.

**Final remarks**

Antimalarials have played a central role in the treatment of CLE over the past several decades. Quinacrine, in particular, has been an important adjutant therapy when a single antimalarial agent is unable to control CLE. Unfortunately, this medication has become increasingly scarce and is currently unavailable in the USA. While there are other local and systemic medications available from several different medication classes, the quality of evidence for these medications can vary, making it difficult for the provider to choose an optimal treatment plan for patients with CLE. In addition, there are new targeted therapies being studied in clinical trials that may one day become available as effective treatment options for CLE. Ultimately, it would greatly benefit patients with CLE to have access to quinacrine as a potential treatment again. However, until this option is available, alternative therapies should be used to maintain control of the disease and prevent any flares or gaps in treatment.

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**Contributors**

DY and RB contributed to the design, drafting, revision and final approval of the manuscript. RDS and VPW contributed to the concept, design, drafting, revision and final approval of the manuscript. DY and RB contributed equally and should be considered cofirst authors.

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**Patient and public involvement**

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Patient consent for publication**

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No additional data are available.

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