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Prescription strategy of antimalarials in cutaneous and systemic lupus erythematosus: an international survey

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Abstract

Background: Antimalarial agents (AMs), mainly hydroxychloroquine (HCQ) and chloroquine, are the cornerstone of treatment of cutaneous and systemic lupus erythematosus. However, many aspects of AM prescription remain empirical. The aim of this study was to assess the modalities of AM prescription among physicians treating patients with lupus and to verify the assumption that AM use is heterogeneous and frequently at variance with international guidelines.

Methods: We performed an international cross-sectional study among physicians involved in lupus care, using a web-based survey (from September 2019 to July 2020) addressing the main controversial aspects of AM prescription.

Results: A total of 298 physicians [median age: 42 (interquartile range: 17) years, mainly internists and rheumatologists] from 35 countries participated to the study. A total of 93% used HCQ as the first-line AM, 69.5% used fixed doses of AMs (mainly 400 mg/day for HCQ) and only 37.9% adjusted the dose in case of renal failure. The main reasons for measuring HCQ blood levels were suspected non-adherence (55.7%) and failure of AM treatment (34.1%). In case of AM failure, 58.0% added an immunosuppressive agent. In case of remission, 49.7% maintained the same dose of AM, whereas 48.3% reduced the dose. One-third of respondents reported not following the American screening guidelines on AM retinal toxicity and 40.9% started retinal screening from the first year of treatment.

Conclusion: This study highlights the strong heterogeneity of AM prescription in lupus, as well as several key unmet needs regarding AMs. This may be improved by developing more comprehensive recommendations and favoring dissemination among physicians.

Keywords: antimalarial agents, care survey, cutaneous lupus erythematosus, health, systemic lupus erythematosus

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Introduction

Antimalarial agents (AMs), mainly hydroxychloroquine (HCQ) and chloroquine (CQ), have become the cornerstone of treatment of cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE).[1] The use of AMs has been associated with numerous beneficial properties, whereas side effects, with the main exception of retinopathy, are generally considered benign, transient or uncommon.[2]

Despite their central role in the management of lupus, the prescription of AMs remains largely empirical. Besides, existing guidelines may not be fully implemented due to controversial issues or insufficient dissemination among physicians. Furthermore, the emergence of recently defined concepts such as remission or lupus low-disease activity state (LLDAS)[3,4] raises new questions about further therapeutic management when these outcomes are achieved.

We conducted an international survey to assess the modalities of AM prescription among physicians treating patients with lupus. Our aims were to verify the assumption that AM use is largely heterogeneous and frequently at variance with international guidelines and to analyze the reasons which may explain such findings. We also sought to identify the unmet needs regarding AM prescription that will need to be addressed in future recommendations.

Methods

Conception and dissemination of the questionnaire

This survey consisted of an online questionnaire (Supplementary Table S1) composed of 17 questions which addressed the following aspects of AM prescription: indication, choice of AM agent to use, dose, prescription in case of renal failure, management of doses in case of remission, management of AM failure, assessment of treatment adherence, retinal toxicity screening and prescription in pregnant and breastfeeding women. We focused on the points that the steering committee (A.P., R.F. and L.A.) thought to be subject to debate among physicians. Questions about respondents' demographics (age, type and country of practice, medical specialty) were also included. The online questionnaire was designed using Google Forms. Dissemination of the questionnaire was facilitated by the following medical societies and reference networks: Société Nationale Française de Médecine Interne, Société Francophone de Néphrologie Dialyse et Transplantation, Centre National de Référence des Maladies Auto-immunes et Systémiques Rares de Strasbourg, European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET) as well as by direct email contact with worldwide physicians involved in the care of patients with SLE.

Statistics

Qualitative variables were described using numbers and percentages and quantitative variables as medians and the 25th–75th percentile interquartile range (IQR). Statistical analysis was performed using JMP 13 (SAS institute, Cary, NC, USA).

Data statement

The data that support the findings of this study are available from the authors upon request.

Ethics

Ethics approval and informed consent were not required for the present study because no patient data was collected.

Results

Participants demographics

Between September 2019 and July 2020, 298 physicians participated to the survey. The median (interquartile range) age of respondents was 42 (17) years. Participants were originating from 35 countries, with a majority from France ($n = 169/296$, 57.1%) (see Supplementary Table S2 for the full list of countries). The medical specialties of the respondents were internal medicine ($n = 181/298$, 60.7%), rheumatology ($n = 98$, 32.9%), nephrology ($n = 14$, 4.7%), dermatology ($n = 3$, 1%) and pediatrics ($n = 2$, 0.7%). Participants worked in academic centers ($n = 201/296$, 67.9%), nonacademic or private hospitals ($n = 73$, 24.7%) or as private practitioners ($n = 22$, 7.4%). Detailed analyses according to age, country, specialty and type of practice are available in Supplementary Tables S3, S4, S5 and S6, respectively.

Survey results

Among the respondents, 294 (98.7%) reported prescribing AMs systematically to all patients with CLE or SLE.

With regard to first-line AM choice, 277 of 298 physicians (93.0%) opted for HCQ and 21 (7.0%) for CQ (none for quinacrine). Reasons reported for prescribing HCQ as the first-line AM agent were (respondents could provide several reasons): a better tolerance profile ($n = 158/277$, 57.0%), better availability ($n = 109$, 39.4%), better efficacy ($n = 79$, 28.5%), lower cost ($n = 30$, 10.8%), more evidence available ($n = 5$, 1.8%), prescription habit ($n = 4$, 1.4%), compliance with guidelines ($n = 3$, 1.1%). No specific rationale was provided by 39 respondents (14.1%). Reasons for prescribing CQ as a first-line treatment were its better availability in the respondent's country ($n = 17/21$, 81.0%), lower cost ($n = 10$, 47.6%) and better efficacy ($n = 1$, 4.8%).

Among the respondents, 291 (97.7%) knew that AMs are compatible with pregnancy and 269 (90.3%) with breastfeeding.

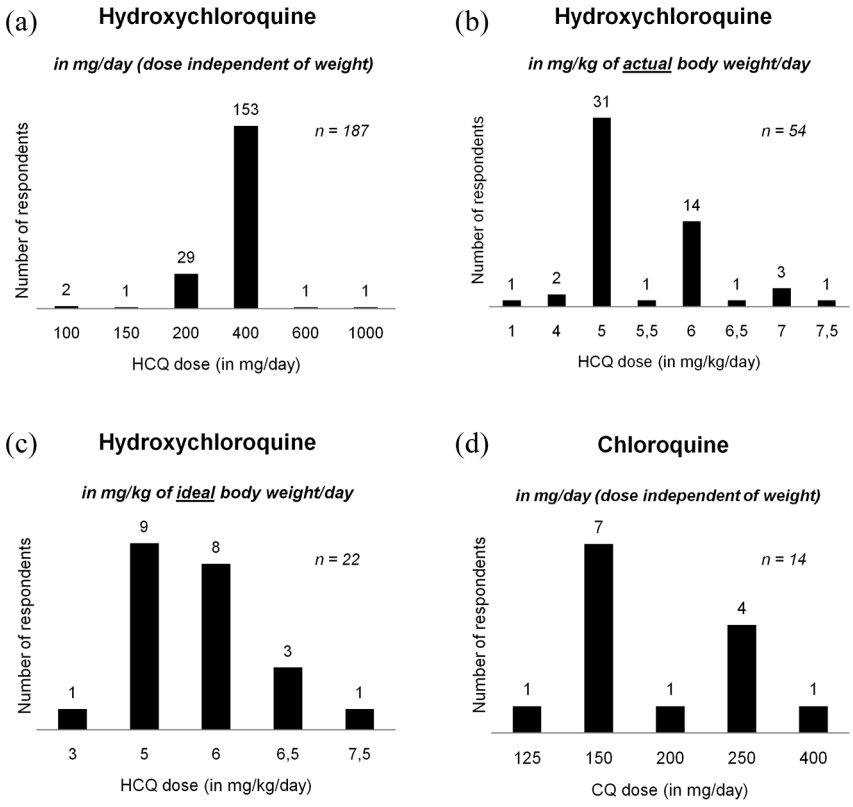

Figure 1. Usual daily doses of hydroxychloroquine and chloroquine.
HCQ doses are reported as fixed doses (a), actual weight-based doses (b), or ideal weight-based doses (c). For CQ, only the fixed doses are shown (d) because only five prescribers determined the dose according to actual or ideal weight.
CQ, chloroquine; HCQ, hydroxychloroquine.

A majority ($n=163/283$, 57.6%) of respondents did not use quinacrine because the drug is not available in their country, 43 (15.2%) used it as an alternative to HCQ or CQ in case of inefficacy, contraindication or intolerance, 35 (12.4%) declared knowing only little or nothing about this drug, 22 (7.8%) did not use it because of efficacy concerns, 6 (2.1%) added it to HCQ or CQ in case of insufficient efficacy, while 14 (4.9%) did not use it without providing a specific reason.

A majority of respondents ($n=207/298$, 69.5%) used a fixed dose of AMs (typically 400 mg/day for HCQ and 150 mg/day for CQ, Figure 1) while 68 (22.8%) used a dose determined according to actual body weight and 23 (7.7%) to ideal body weight.

In case of renal failure, only 113 of 298 participants (37.9%) adjusted the AM dose according to the estimated glomerular filtration rate (eGFR), 91 (30.5%) did not think/knew that a dose adjustment may have been needed, 53 (17.8%) used HCQ blood levels to adjust the dose and 41 (13.8%) did not know how to adjust the dose in case of renal failure. The eGFR below which respondents ($n=99$) usually reduced the dose were: 80 ml/min ($n=1$, 1.0%), 60 ml/min ($n=22$, 22.2%), 50 ml/min ($n=1$, 1.0%), 45 ml/min ($n=1$, 1.0%), 40 ml/min ($n=2$, 2.0%), 30 ml/min ($n=57$, 57.6%), 25 ml/min ($n=2$, 2.0%), 20 ml/min ($n=6$, 6.1%) or 15 ml/min ($n=7$, 7.1%).

The methods employed to assess therapeutic adherence to AMs were (several possible answers): to ask the patient directly whether the treatment is taken or not ($n=253/297$, 85.2%), to measure HCQ blood levels ($n=136$, 45.8%), to use an adherence questionnaire ($n=20$, 6.7%), to check with the pharmacy if the medication has been picked up ($n=4$, 1.3%). Only 12 respondents (4.0%) declared not to assess therapeutic adherence.

Participants measured HCQ blood levels in case of (several possible answers): suspected nonadherence

($n=165/296$, 55.7%), flare and/or absence of response to AM ($n=101$, 34.1%), randomly or without any specific context ($n=68$, 23%), at each visit ($n=6$, 2.0%), in case of renal or hepatic failure ($n=4$, 1.4%), when AM toxicity was suspected ($n=1$, 0.3%), when discussing a dose reduction ($n=1$, 0.3%), at first visit after HCQ introduction ($n=1$, 0.3%), at least once a year ($n=1$, 0.3%), or in case of extreme weight ($n=1$, 0.3%). Among the respondents, 131 (44.3%) did not measure HCQ blood levels, either because of the unavailability of the method in their center ($n=102$, 34.5%) or because they did not consider it useful ($n=29$, 9.8%).

In case of failure of a first-line of AM treatment, and assuming nonadherence had been excluded, respondents would typically add an immunosuppressive agent ($n=170/293$, 58.0%), measure HCQ blood concentrations and increase the dose if needed ($n=98$, 33.4%), switch to another AM ($n=10$, 3.4%), transiently increase the AM dose irrespective of blood levels ($n=9$, 3.1%), combine two AMs ($n=4$, 1.4%), transiently increase the AM dose while adding another agent ($n=1$, 0.3%), measure HCQ blood concentrations and add another drug only in case of clinical emergency ($n=1$, 0.3%).

In case of sustained remission, 148 of 298 physicians (49.7%) maintained the same dose of antimalarial indefinitely, 144 (48.3%) reduced the dose and 6 (2.0%) discontinued AMs. For a large majority of respondents (78.6%, $n=99/126$), the usual reduced dose of HCQ was 200 mg/day. The typical duration of remission after which participants chose to reduce or stop antimalarials were as follows: 6 months ($n=32/147$, 21.8%), 12 months ($n=38$, 25.8%), 24 months ($n=39$, 26.5%), 36 months ($n=12$, 8.2%), 48 months ($n=6$, 4.1%), 60 months ($n=12$, 8.2%), or other durations ($n=8$, 5.4%).

Among respondents, 122 (40.9%) were aware of the 2016 American Academy of Ophthalmology (AAO) guidelines on AM retinal toxicity and reported following them, 36 (12.1%) were not aware of those recommendations, 34 (11.4%) were aware of those recommendations but disagreed with their appropriateness and 24 (8.1%) followed local or national guidelines instead. Of note, 82 respondents (27.5%) let the ophthalmologist choose the adequate screening method and frequency of follow-up. The reasons given by the participants who judged the AAO guidelines inappropriate were preference for annual screening since the beginning of treatment ($n=11$), recommended maximum doses considered too low ($n=4$), recommended doses based on tolerance and not on efficacy data ($n=1$), actual toxicity being less important according to registries than what is presented in the recommendations ($n=1$).

Regarding the retinal toxicity of AMs, participants planned the initial ophthalmic evaluation as follows: before initiation of AM ($n=63/298$, 21.1%), within the first 3 months of treatment ($n=130$, 43.6%), within the first 6 months ($n=2$, 0.7%), within the first year ($n=100$, 33.6%). Only a few ($n=3$, 1.0%) respondents did not consider the initial ophthalmic evaluation required.

The typical frequency of retinal screening during AM treatment was: every 6 months from the beginning of treatment ($n=5/296$, 1.7%), every 6 months after 5 years ($n=3$, 1.0%), annually from the beginning ($n=121$, 40.9%), annually after 3 years ($n=1$, 0.3%), annually after 5 years ($n=107$, 36.1%), every 2 years from the beginning ($n=21$, 7.1%), every 2 years after 5 years of follow-up ($n=8$, 2.7%), every 18–24 months during the first 5 years and then annually ($n=1$, 0.3%).

Discussion

In this international study, we assessed the modalities of AM prescription by a large sample of physicians involved in lupus care.

Nearly all respondents prescribed AMs to every patient with lupus, provided there was no contraindication. This is in accordance with the international guidelines[5] and is justified by the largely favorable benefit–risk ratio of AMs in lupus.[2]

A vast majority of participants prescribed HCQ rather than CQ or quinacrine as their first-line AM. The two main reasons for preferring HCQ were its better tolerance profile and its better availability in respondents' countries. Data from the literature indeed suggest a lower toxicity of HCQ compared to CQ, especially regarding retinal toxicity.[2,6,7] Among those who preferred HCQ, 28.5% explained their choice by a presumed better efficacy but it is important to note that available data do not support this belief.[6,8] Conversely, prescribers who favored CQ as the first-line AM did it mainly for economic reasons.

Thus, in the large majority of cases, physicians followed the European League Against Rheumatism (EULAR) guidelines to prefer HCQ as first-line AM[5] due to its better benefit–risk ratio, except when there was a lack of access to this drug.

Only about 15% of respondents reported using quinacrine, either as an alternative to HCQ or CQ or, less frequently, in addition to those AMs. None of them used quinacrine as a first-line treatment. Thanks to a partially distinct mechanism of action,[9] quinacrine, also known as mepacrine, has demonstrated significant efficacy, alone or in association to other AMs, for treating CLE cases refractory to HCQ or CQ.[10,11] Moreover, retinal toxicity does not occur with quinacrine, which makes it an interesting alternative in case of ophthalmologic contraindication to the use of other AMs. Accordingly, the 2016 European guidelines on CLE recommend adding quinacrine when the first-line systemic treatment (i.e. HCQ monotherapy) fails.[12] In the 2019 updated EULAR recommendations for the management of SLE, the use of quinacrine is suggested in 'patients with cutaneous manifestations and HCQ-induced retinal toxicity'.[5] However, because of serious concerns about its tolerance profile (aplastic anemia and drug-induced hepatitis),[13–15] quinacrine has been withdrawn from the market in several countries. This could explain the infrequent use of quinacrine reported in our study. Other reasons might include the lack of detailed knowledge about this drug, the fear of adverse events, as well as the limited data available on its benefits outside of CLE.

About 70% of respondents used a fixed dose of AMs (independent of the patient's weight). By contrast, the latest EULAR and AAO guidelines recommend the use of actual weight-based doses.[5,16] Less than 10% used ideal weight-based doses while this is no longer recommended because it is thought to be less correlated with the risk of retinopathy.[17] The most commonly reported daily dose of HCQ was 400 mg, which interestingly exceeds the maximum recommended dose of 5 mg/kg/day for any patient weighing less than 80 kg. Noteworthy, the AAO has reduced the recommended daily dose of HCQ from 6.5 to <5 mg/kg/day in 2016,[16] based on a 2014 study by Melles and Marmor,[17] which showed a risk of retinopathy higher than previously reported (<1% up to 5 years, <2% up to 10 years and almost 20% at 20 years, for a daily dose between 4 and 5 mg/kg). It should be noted that this unexpectedly high incidence may simply be a consequence of the better sensitivity of newer screening methods. Furthermore, Petri *et al.*[18] found an incidence of retinopathy of less than half of that reported in the above-mentioned study, using a maximum HCQ daily dose of 400 mg and reducing the dose in high-risk patients. Two additional criticisms were raised against the maximum dose of 5 mg/kg/day recommended by the AAO for HCQ. First, the study by Melles and Marmor did not analyze prescribed doses but pharmacy-dispensed medications, yet the latter may have been lower than the former because of nonadherence, which is common in SLE. Second, and most importantly, it remains unknown whether the lower recommended dose of HCQ would have the same efficacy, since HCQ benefits in lupus have been shown in studies conducted when the recommended dose was 6.5 mg/kg/day. These limitations, as well as the delay before the implementation of recently issued guidelines, may explain the discrepancies between recommendations and real-world practice. Of note, survey respondents who determined the AM dose according to actual weight followed in their majority the recommended dose of 5 mg/kg/day. CQ users also favored fixed doses, with 150 mg/day and 250 mg/day being the first and second most commonly prescribed doses, respectively. This is to be compared with the maximum daily dose of CQ suggested by the AAO, which has been set at 2.3 mg/kg because of its equivalence to 5 mg/kg of HCQ.

Although the grade of the recommendation is low, the recent joint EULAR and European Renal Association–European Dialysis and Transplant Association recommendations on lupus nephritis advise a 50% reduction in the dose of HCQ for patients with eGFR <30 ml/min.[19] Interestingly, less than 40% of the participants in our survey reported adjusting the AM dose according to renal function, a majority of those (58%) under 30 ml/min as recommended. It should be noted that 80% of participants answered to the survey before the publication of these guidelines. However, dose adjustment in patients with renal failure had previously been suggested[20] due to the excretion of HCQ by the kidneys and the increased risk for HCQ-associated retinal toxicity in patients with renal failure.[17,21]

Therapeutic nonadherence is common in chronic diseases, and lupus is no exception.[22,23] Recognition

of nonadherent patients is primordial because it avoids the inappropriate attribution of ongoing lupus activity to the failure of AMs and thereby prevents the potentially deleterious addition of an immunosuppressive agent. Asking patients directly whether or not the drug is taken is a simple, fast and inexpensive way to assess compliance which most of respondents used, yet has been shown largely insufficient when used alone.[22,24] Low HCQ blood concentrations have been shown to be a reliable marker of nonadherence,[22] with increased accuracy compared to patient self-report,[24] and correlate well to pharmacy refill data.[23] The 2019 EULAR recommendations suggest the use of drug blood levels to assess compliance, which about 50% of respondents actually did. Of note, the use of more time-consuming methods such as adherence questionnaires or the assessment of drug dispensation by pharmacies was anecdotal. The second main circumstance associated with the measurement of AM blood levels was failure of AM therapy. A concentration–effect relationship for HCQ, both in terms of efficacy and ocular toxicity, has been established in CLE and SLE.[25,26] Also, a major between-patients variability of HCQ blood levels has been demonstrated.[27] Therefore, measuring HCQ blood levels could help identify patients in whom AM treatment failed because of low blood concentrations despite optimal therapeutic adherence. Finally, it is important to note that most respondents who did not use HCQ blood levels did not have access to such measurement in their centers.

In case of AM failure, most of respondents (58%) added an immunosuppressive agent (provided nonadherence had been excluded). However, in the aforementioned patients who have low blood HCQ concentrations despite being compliant, it could be of interest to first increase the AM dose before adding immunosuppressive agents or biotherapies. Of note, this attitude was favored by one-third of respondents. Costedoat-Chalumeau *et al.*[28] suggested the value of 1000 ng/ml as the target blood HCQ concentration because it showed the best tradeoff between sensitivity and specificity for the prediction of flare in the subsequent 6 months. However, the prospective validation of this strategy in a placebo-controlled clinical trial[29] did not reach its primary endpoint (i.e. a lower number of patients with flares during a 7-month follow-up). On the contrary, a threshold of 750 ng/ml had been prospectively validated in CLE, but the sample-size was limited.[30] A blind increase in the AM dose, an option that the respondent panel exceptionally chose, but that physicians for whom drug monitoring is not available might find attractive, should be done with caution as this may result in supra-therapeutic blood levels and increased toxicity. Lastly, and as mentioned above, the switch for another AM or the combination of two AMs (namely HCQ or CQ plus quinacrine) is common practice in CLE and usually precedes the use of other classes of drugs.

The respondents were divided about the management of AMs in case of remission. About one-half used AMs at the same dose, whereas the other half reduced the dose (most often to 200 mg/day for HCQ prescribers). Only a small minority (2%) stopped AMs. The delays after which physicians reduced or stopped the AM were highly variable, highlighting the lack of clear consensus. Although very few studies have investigated the effect of AM withdrawal in case of remission,[31,32] current guidelines indicate that HCQ should be continued indefinitely throughout the course of the disease, provided toxicity does not occur.[2] To the best of our knowledge, the feasibility of reducing the dose of AMs during remission has not been studied in any randomized trial; nevertheless, the 2019 EULAR recommendations for the management of SLE suggest the possibility to do so in patients with long-standing remission.[5] However, both the definition of long-standing remission and the recommended reduced dose are not explicitly mentioned in those recommendations. This probably explains why physicians are so divided on this question.

Interestingly, almost one-third of respondents reported not following the AAO guidelines on AM retinal toxicity.[16] The main reasons were the use of other (local or national) guidelines, the lack of knowledge of the AAO recommendations or their presumed inappropriateness. Beside the issue of the recommended doses that we have already discussed, another point of disagreement was the frequency of ophthalmologic screening. A small majority of respondents started screening from the first year of treatment instead of the recommended 5 years. This decision is debatable in people without additional risk factors for AM-induced maculopathy since early toxicity is exceptional in this population.[17,33] It is different in high-risk patients for whom screening is advised after the first year of treatment. It should be pointed out that a daily dose of HCQ >5 mg/kg is one of the major risk factors for retinal toxicity. Because many respondents use such doses, early screening may still fall within AAO guidelines.

It is well established that AMs are compatible with pregnancy and breastfeeding,[2,34] as most physicians are aware. It is important to underline that AM prescription is recommended in pregnant women with SLE,[35] as it decreases the risk of adverse maternal and fetal outcomes.[36–38]

This study has some limitations. Although survey respondents were originating from all over the world, a great majority were from France. Also, participants were not as numerous as initially hoped for, which is a common situation in surveys based on voluntary participation. These two points may have limited the external validity of the results. In addition, the risk of declaration bias is inherent to declarative studies and cannot be ruled out. Finally, it would have been relevant to know the respondents' experience in lupus management (through years of practice and number of lupus patients seen per month); however, participants were not asked for this information.

Overall, our survey highlights the generally heterogeneous prescription of AMs. Although several recommendations have been issued in the recent years, our results underline the need for clarifying certain aspects of AM prescription, such as the optimal use of HCQ blood levels, management of AM monotherapy failure and adaptation of AM treatment during remission and LLDAS. Of note, the heterogeneity of AM use also pertains to topics that have already been addressed by current guidelines. This may have been related either to the reluctance of some prescribers to apply those recommendations because of debatable issues,[1] or to a lack of knowledge which may have been the consequence of insufficient dissemination. Finally, physicians practicing in low-income countries may have limited access to some of the recommended options.

To conclude, this study emphasizes the need to further investigate critical aspects of AM prescription in well-designed prospective lupus studies and to develop more comprehensive evidence-based recommendations. It also supports the need to discuss further the debated items of existing recommendations as well as to provide a better dissemination of current and future guidelines.

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Conflict of interest statement

Arthur Petitdemange declares no competing interest.

Renaud Felten has participated to Advisory Boards for Abbvie, Novartis and received invitations or performed interventions for Abbvie, BMS, Lilly, Nordic, Novartis, MEDAC, MSD, Pfizer, Sanofi and UCB.

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Supplemental material

Supplemental material for this article is available online.

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