The importance of assessing medication exposure to the definition of refractory disease in systemic lupus erythematosus

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Abstract

Treatment of patients with Systemic Lupus Erythematosus (SLE) who have active disease refractory to current therapeutic strategies continues to be a real challenge. Here, we propose that the classic definition of refractory SLE patients – failure to achieve adequate response to the standard of care – should be further refined to incorporate the dimension of adequate drug exposure. Inter-individual pharmacokinetic variability may induce insufficient exposure to many drugs used in SLE, leading to both apparent inefficacy of treatments and inappropriate therapeutic escalation. Among others, we have shown that individual assessment of exposure to mycophenolic acid, the active metabolite of mycophenolate mofetil (MMF) could be used to determine whether a given patient received adequate doses of MMF. We have also shown that measuring blood concentrations of hydroxychloroquine could be used as an efficient way to assess observance, which is a critical issue since a significant proportion of refractory SLE patients is likely to have poor observance as the primary source of treatment failure. Finally, we have underlined the importance of assessing drug interactions as SLE patients often require, in addition to immunosuppressants, several other drugs to prevent or treat associated conditions, which may result in decreased exposure to immunosuppressants.

Considering these data, we believe that refractory SLE patients should not only be defined as the failure to achieve adequate therapeutic response to the standard of care, but should also incorporate the dimension of inadequate pharmacokinetic exposure and include drug blood level, interaction and observance monitoring.

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1. Introduction

Recent advances in our understanding of the pathophysiology of systemic lupus erythematosus (SLE) have offered new therapeutic perspectives [1,2]. Current treatment options for SLE mostly include antimalarial drugs, steroidal and nonsteroidal anti-inflammatory agents,
immunosuppressive drugs including methotrexate, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil (MMF), and biologics [3]. While there has been a dramatic improvement in the prognosis of SLE during the past decades [4], a substantial subset of these patients still fail to achieve optimal disease control despite what is currently defined as “the standard of care” for SLE.

A critical issue to define refractory disease is to ensure that patients have been adequately exposed to the drugs prescribed in SLE [5]. Indeed, too little exposure may lead to an ineffective drug regimen and to an inappropriate therapeutic escalation [6]. The definition of refractory SLE should thus be further refined to incorporate the crucial dimension of adequate drug exposure.

2. Assessing adequate exposure to drugs used in SLE patients

High inter-individual pharmacokinetic variability may likely induce insufficient exposure to some of the drugs used in SLE and variation in the treatment response [5,7]. Indeed, several drugs are given at a fixed dose while their disposition (absorption, distribution, metabolism, and excretion) is strongly affected by multifactorial (environmental, genetic, and disease-specific) determinants which may impair their bioavailability [6]. These pharmacokinetic concepts have been originally developed in solid-organ transplantation, where they have contributed in improving patients’ outcomes by optimizing therapeutic strategies [8,9], and are now being transposed for the management of patients with auto-immune disease. For instance, MMF is widely used in SLE at a fixed dose of 2 or 3 g/day [10–14]. It is an inactive prodrug (Fig. 1) that is first converted into its active metabolite (Mycophenolic acid, MPA) by intestinal, liver and plasma esterases [15]. Then, MPA inhibits the activity of the target enzyme Inosine MonoPhosphate DeHydrogenase (IMPDH) [16]. Among others, we have recently underlined that these steps were subjected to a very high inter-individual pharmacokinetic variability [5,17–21]. Thus, using a fixed dose of MMF guarantees neither proper exposure to its active metabolite, MPA, nor proper inhibition of its final target, IMPDH. Thus, assessment of MPA exposure is of major importance, as it is the only way to ensure that SLE patients receive an individualized dose of MMF that meets their unique pharmacokinetic variability. In a recent cross-sectional study of 71 consecutive SLE patients [5], we observed a 10-fold variation of the exposure to MPA per gram of MMF given (Fig. 2), using the area under the plasma concentration-time curve from 0 to 12 h after administration of MMF (MPA AU C0–12 h), which is the pharmacokinetic parameter that has the best relationship with clinical outcome in solid organ transplant patients [8,9]. This is a very important issue as this study revealed on a large cohort of SLE patient that the pharmacokinetic variability of MMF had a direct biological consequence as it led to a marked underexposure in many patients. In this study, we further found that the mean MPA AU C0–12 h of patients with active SLE was significantly lower than that of patients with inactive SLE, and that MPA AU C0–12 h correlated with the SLEDAI as well as with C3 and anti-dsDNA levels [5]. This further suggests that the high pharmacokinetic variability of MMF has a direct clinical impact on disease activity in SLE, and thus should be taken into account. Finally, we have shown that an MPA AU C0–12 h above 35 µg.h/ml was associated with the lowest risk of active SLE, as assessed by both the SLEDAI (score ≥ 6) and the BILAG index (BILAG A and B). Although additional prospective studies are now needed for the formal validation of this threshold, our data suggest that using tailored therapeutic strategies with an MPA AU C0–12 h above 35 µg.h/ml may be a promising way to improve SLE treatment and to decrease the number of so-called refractory SLE patients. Other groups have observed similar findings in SLE patients treated with MMF. In a study of 20 patients, Roland et al. [18] have shown that MPA AU C0–4 h levels tended to be lower in SLE patients who had low C3 and C4 complement fractions, as well as in patients who had increased anti-dsDNA levels. This further suggests that there is a relationship between exposure to MPA and disease activity in SLE. In a recent study of 19 SLE patients, Sagcal-Gironella et al. have shown [19] that MPA AU C0–12 h and weight-adjusted MMF dosing were moderately correlated, and that an MPA AU C0–12 h of ≥ 30 µg.h/ml – a threshold very similar to what we observed – was associated with a significant decrease in BILAG scores while on MMF therapy. Thus, one key message of this study is that the high pharmacokinetic variability of MMF makes it difficult to predict the amount of MPA a given patient will be exposed to a given dose of MMF. The logical consequence is that MPA exposure should be measured in SLE patients treated with MMF, in order to ensure proper exposure to the active metabolite. Finally, Lertdumrongluk et al. [17] have shown that the mean MPA AU C0–12 h observed in a cohort of 7 patients with class III or IV lupus nephritis who were considered non-responders after 6 months of mycophenolate therapy – either MMF or enteric-coated-mycophenolate sodium – was significantly lower than that observed in 11 responders. Responders and non-responders were comparable in age, body mass index, duration of lupus nephritis, and disease activity. In this study, the MPA AU C0–12 h that best distinguished responders from non-responders at 6-months was 45 µg.h/ml, a slightly higher value than that we found in our cross-sectional study.

Altogether, these findings underline the fact that high interindividual variability of MMF pharmacokinetics is a key parameter of the response to MMF. They suggest that one should ensure that the so-called

![Fig. 1. Pharmacokinetic variability of mycophenolate mofetil and hydroxychloroquine in SLE. Distribution of AU C0–12 h of mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil, for 1 g of MMF given (left panel) and hydroxychloroquine plasma concentrations for 200 mg given (right panel) is shown for 71 and 100 patients with systemic lupus erythematosus, respectively. These data underline the high inter-individual pharmacokinetic variability of these two drugs in SLE.](image-url)
refractory SLE patients treated with MMF have proper exposure to MPA before being considered truly refractory patients, and that a threshold of at least 30 to 45 mg h/L should be reached in order to better control disease activity.

Hydroxychloroquine (HCQ) is another drug that is given at fixed dose to SLE patients (400 mg/day is the most common dose). Similar approaches as those developed for MMF may be used for HCQ, as strong inter-individual variations in blood HCQ concentrations have also been reported in SLE patients receiving HCQ (Fig. 2), and SLE disease activity is higher in patients with low blood HCQ levels [7]. Indeed, in a study conducted by our group the mean whole-blood HCQ concentration observed in 23 patients who had active disease at baseline was significantly lower than the one measured in 120 patients with inactive disease (694 ± 448 ng/ml versus 1079 ± 526 ng/ml, p = 0.001), even after exclusion of non-observant patients. Thus, concentrations of HCQ may be used not only as a marker of non-adherence but also as a way to predict response to treatment in SLE [7]. This indirectly underlines that inter-individual variability of drug metabolism is a major source of treatment failure [22], and should be considered, when possible, in all refractory patients with SLE.

### Table 1
Pharmacokinetic parameters of main drugs used in SLE.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Active metabolite</th>
<th>Plasmatic half-life</th>
<th>May be used in SLE for</th>
<th>Observance assessment</th>
<th>Exposure assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone/prednisolone</td>
<td>Prednisolone</td>
<td>3.4–3.8 h</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Methotrexate</td>
<td>≈ 2 h</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Azathioprine (AZA)</td>
<td>6-Mercaptopurine</td>
<td>30–60 min</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Hydroxychloroquine</td>
<td>&gt;40 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4-Hydroxycyclophosphamide</td>
<td>4–7 h</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Mycophenolic acid (MPA)</td>
<td>8–16 h</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Fig. 2. Metabolism of mycophenolate mofetil. MMF is usually given at a fixed dose of 2 or 3 g/day in SLE. It is an inactive prodrug that is first converted into its active metabolite (Mycophenolic acid, MPA) by intestinal, liver and plasma esterases. Then, MPA inhibits the activity of the target enzyme Inosine Monophosphate Dehydrogenase (IMPDH).

3. Assessing blood concentrations of drugs as markers of non-adherence in SLE patients

Former U.S. surgeon general C. Everett Koop is often quoted as saying, “Drugs don’t work in patients who don’t take them.” [23]. Indeed, poor adherence to therapeutic regimens is a major issue in patients with chronic diseases. Rates of non-compliance in SLE are known to range from 10% to 70% [24–28]. Thus, a significant proportion of so-called refractory SLE patients is likely to have poor observance as the primary source of treatment failure. Among the many ways that may be used for assessing adherence to treatment [23], unscheduled measurement of drug blood levels is one of the easiest and more objective methods. Unfortunately, the drugs that may be used for such assessment are limited in SLE, because only those that are not only widely used but also have long elimination half-lives may be used for this purpose (Table 1). Recently, our group has evaluated the possibility of using assessment of blood hydroxychloroquine (HCQ) concentrations as a marker of poor adherence to treatment in SLE [29]. Indeed, HCQ and its metabolite levels can now be routinely quantified using high performance liquid chromatography (HPLC), which is a widely available method. Because of its long
terminal elimination half-life (≈40 days), patients with low blood HCQ concentrations have undoubtedly failed to take HCQ (and presumably others SLE medications) for a long time. Thus, the assessment of HCQ concentration may be used as a marker of non-compliance. In a study of 203 unselected patients receiving long-term care for SLE [29], unscheduled blood HCQ concentrations were measured, and the physicians provided the patients with the HCQ assay results while interviewing them non-judgmentally. Patients were classified as non-compliant if they admitted they had stopped HCQ or taken it only rarely in the preceding weeks. Fourteen patients (7%) confirmed their poor adherence in these interviews, during which they were confronted with their blood HCQ levels. Blood HCQ concentrations were undetectable in 8 patients and ranged from 10 to 129 ng/ml in 6, with a mean ± SD blood HCQ concentration of 26 ± 46 ng/ml versus 1079 ± 473 ng/ml (range 205–2629) in the 189 compliant patients. Interestingly, these 14 patients all denied non-compliance until shown their blood HCQ results. Physicians treating 9 (64%) of these 14 patients did not suspect non-compliance, a finding not totally surprising as clinical judgment has been found wanting in almost every study in which it has been examined [23]. Indeed, during the previous year, 12 of the 14 noncompliant patients had come regularly to their routine appointments, without missing any, all had regularly undergone their routine yearly electroretinogram from onset of HCQ treatment, and none reported difficulties with treatment adherence. Importantly, the clinical consequences of such non-compliance were substantial, as low blood HCQ concentrations at baseline were strongly associated with ongoing disease activity and, in patients with inactive SLE at baseline, with the risk of further SLE flares during the following 6 months [7]. This further suggests that poor compliance should be considered a major cause of treatment failure in SLE. Thus, monitoring blood HCQ levels (which is available within a few days in our center) may be used as a valuable tool by doctors managing SLE flares, as this may help determine whether active disease is due to a lack of response to the standard of care (i.e., a true refractory patient) or to poor compliance. Misinterpretation of non-compliance is extremely important since it usually leads to an unnecessary therapeutic escalation. Altogether, these data underline the importance of incorporating the assessment of non-compliance into the definition of refractory patients in SLE, as an individual patient should not be considered refractory until it is clearly proven that he has adequate therapeutic observance.

4. Assessing drug–drug interactions

Another key aspect one should consider when managing refractory SLE patients is drug interactions [6], as the result of such interactions may be increased or decreased exposure to the active metabolite or toxicological effect [30]. SLE patients often require, in addition to immunosuppressants, several other drugs to prevent or treat associated conditions such as hypertension, hyperlipidemia, gastroduodenal ulcer, osteoporosis, and infections. Several of these drugs such as calcium-channel blockers, statins, proton-pump inhibitors, azole antifungal agents and macrolide antibiotics, among many others, are known to interact with the drugs commonly used in SLE and may strongly impair their bioavailability [31,32]. For instance, a recent study has shown that heart transplant recipients with proton-pump inhibitor comedication during MMF therapy have significantly lower exposure to mycophenolic acid [31]. Although the clinical relevance of this pharmacokinetic interaction was not determined in the study, it is very likely that drug interactions account for a significant proportion of treatment failures. Thus, the physicians should keep in mind that drug interaction is a common problem that should be considered in all refractory patients as it may decrease the exposure to the immunosuppressants and result in treatment failure despite an adequate observance [31,32].

5. Refining definition of refractory SLE by incorporating the real drug exposure dimension

Based on the previous findings, we believe that refractory SLE patients should be defined as the failure to achieve optimal disease control using the standard of care, but only after adequate pharmacokinetic exposure to drugs has been assessed and poor compliance has been ruled out. This should include a comprehensive search for interactions among all the medications prescribed as well as for herb–drug and food–drug interactions [33]. In patients in whom pharmacologic assessment of compliance cannot be used, physicians should further seek more indirect clues of adequate observance, such as presence of a cushingoid appearance, lymphopenia, basopenia and eosinopenia in patients taking corticosteroids, or the common finding of macrocytosis in patients treated with azathioprine.

Because drug monitoring is still an emerging field in SLE, future studies should focus on the development of new pharmacological or pharmacogenomic tools aiming at defining more individualized therapeutic strategies, as more tailored treatments could be valuable contributions to the management of SLE.

Conflict of interest

We have no conflict of interest to declare.

Take-home messages

- Treatment of SLE patients refractory to current therapeutic strategies is still a real challenge.
- Inter-individual pharmacokinetic variability may lead to drug inefficacy.
- Exposure to mycophenolic acid can be used to determine whether patients receive adequate doses of MMF.
- Measuring blood concentrations of hydroxychloroquine can help assessing observance.
- Refractory SLE patients should be defined as the failure to achieve disease control using the standard of care after adequate pharmacokinetic exposure to drugs has been assessed.

Acknowledgments

None.

References

Enterovirus infection and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies

To review the association between current enterovirus infection diagnosed with molecular testing and development of autoimmunity or type 1 diabetes. Yeung WC, et al. (BMJ 2011; 342: 35) by means of performing systematic review and meta-analysis of observational studies, analysed with random effects models. PubMed (until May 2010) and Embase (until May 2010), no language restrictions, studies in humans only; reference lists of identified articles; and contact with authors. Study eligibility criteria Cohort or case-control studies measuring enterovirus RNA or viral protein in blood, stool, or tissue of patients with pre-diabetes and diabetes, with adequate data to calculate an odds ratio and 95% confidence intervals. As result, 24 papers and two abstracts (all case-control studies) that met the eligibility criteria included 4448 participants. Study design varied greatly, with a high level of statistical heterogeneity. The two separate outcomes were diabetes related autoimmunity or type 1 diabetes. Meta-analysis showed a significant association between enterovirus infection and type 1 diabetes related autoimmunity (odds ratio 3.7, 95% confidence interval 2.1 to 6.8; heterogeneity $\chi^2$/df = 1.3) and clinical type 1 diabetes (9.8, 5.5 to 17.4; $\chi^2$/df = 3.2). There was a clinically significant association between enterovirus infection, detected with molecular methods, and autoimmunity/type 1 diabetes. However larger prospective studies would be needed to establish a clear temporal relation between enterovirus infection and the development of autoimmunity and type 1 diabetes.