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RESEARCH ARTICLE

Towards Adaptive Structuring of the Lupologist's Consultation to Transform the Care Pathway of Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, which can be clinically heterogeneous in the same patient over the disease process and has an unpredictable evolution. Although its prevalence is increasing, SLE remains a rare disease with frequent extra-articular manifestations managed by multiple specialists. Among these, the internist is a key player in the overall coordination of the care pathway. The dramatic improvement in the short-term prognosis of SLE observed over the past few decades has favoured the emergence of more chronic disease-associated morbidities, especially infectious, cardiovascular and/or related to sequelae, notably renal. Thus, every lupologist is confronted with the difficulty of having to address, in an educational, individualised but also systematic way, a certain number of key items on which the short-, medium- and long-term medical future of patients who develop SLE at a relatively young age depend. In recent years, in addition to the creation of a network of reference centres and the drafting of regularly updated national therapeutic guidelines and therapeutic education programs, international consensus about the factors to consider in SLE patients has been reached, including the definition of therapeutic objectives according to a treat-to-target (T2T) strategy. However, the translation of these new objectives/paradigms in real-life has encountered a number of difficulties. As part of a multidisciplinary team involving SLE patients, we developed practical tools in the form of CHECKLISTs addressing the problems of refractory SLE (D2T), the management of comorbidities and toxicities (BASICs), and, more recently, therapeutic de-escalation with a shared medical decision (T2U). It appears that there is an opportunity to transform the care pathway of SLE patients by allowing the implementation of these tools within adaptive structuring of the consultation, which has the advantage of defining a starting point within the care pathway as a common denominator for lupologists, regardless of their specialty or where they work.

Introduction

Systemic lupus erythematosus (SLE) is a chronic disease. Although this statement may seem obvious since the survival of SLE patients has improved significantly over the past 50 years, it is regularly noted that the management of issues other than those directly related to SLE activity and therapeutics is often disregarded.[1] Indeed, chronicity is accompanied by morbidity and mortality whose expression and causes have changed,[2] involving not only sequelae from severe and/or poorly controlled SLE but also the iatrogeny of treatments administered long-term, whether direct (e.g. infectious) or through associated comorbidities (e.g. cardiovascular).

Although it is a rare condition, SLE has benefited from improvements in the care of more common rheumatic autoimmune conditions such as rheumatoid arthritis (RA). However, SLE has specificities that preclude direct transposition. First, SLE usually begins at a younger age (between 20 and 30 years), stressing the need to carefully consider the balance between disease activity and iatrogeny-comorbidities,[3] which converge with the occurrence of damage and are often intertwined during the follow-up of SLE patients. Unlike RA, where the therapeutic revolution was first biological and then conceptual, the standard treatment for SLE has seen few changes with few biologics approved or used so far.[4] Of course, this does not prevent and even encourages a transformation to global management and allows us to propose a conceptual framework for an optimised SLE care pathway, that will be ready to welcome future innovations.[5] Finally, SLE is a heterogeneous disease, with frequent extra-articular involvement, between patients as well as in the same patient during the course of their disease, and this framework has to be tightly modulated by individual patient characteristics and the evolution of disease status.

In this way, the conceptual transposition performed in recent years defines therapeutic objectives such as remission or low activity, introducing a "treat-to-target" (T2T) approach whose success has been demonstrated in RA.[6] For SLE, this approach should help guide the management of treatment and better define refractory or "difficult to treat" (D2T) SLE. However, alongside the T2T strategy, aimed at achieving and maintaining a "sufficiently good" remission,[7-9] which could benefit from the development of more effective therapies,[5] the prevention of toxicities/damage related to the long-term use of treatments should also be a priority long-term as well as the management of comorbidities, whether pre-existing or induced by these treatments. Therapeutic education programs (TEPs) developed in many centres make it possible to address these aspects in a relevant way. Finally, an axis of prevention is based on the possibility and need to reduce or even stop certain treatments, including but not limited to corticosteroids, when disease control allows it. This involves regular reassessment or "tight control" and ideally a medical decision shared with the patient to secure this process.

There is a clearly identified need to transform the care pathway of SLE patients. In

this narrative review, it seemed interesting to report in a pragmatic way proposals on the structuring of the lupologist's consultation according to the following three axes: (i) control of the disease through a T2T strategy with a specific focus on D2T patients; (ii) screening for frequent toxicities and comorbidities through therapeutic education; and (iii) regular assessment of the feasibility of therapeutic de-escalation, as early and complete as possible, as a new paradigm termed "think-to-untreat" (T2U).[10] For each of these axes we will try to propose tools developed within an ongoing multidisciplinary reflection with and for SLE patients.

Axis n°1: Treat to target (T2T) and Difficult to treat (D2T)

Optimisation and personalisation of SLE treatments are an important part of the consultation. Treatment of SLE is based on a "graduated response" strategy adapted to the severity of the disease and the therapeutic response, as specified in national therapeutic guidelines (PNDS).[11] A distinction is made between the remission-induction phase (treatment of the relapse or attack) and the remission-maintenance phase (maintenance treatment or background treatment). In this article, it is not intended to address these aspects in detail, but to briefly recapitulate principal aspects and recent modification in the therapeutic armamentarium concerning the main therapeutic classes: (i) immunosuppressants (IS): reduction of cyclophosphamide dose (so-called "Euro-Lupus" regimen) to promote tolerance while preserving efficacy in renal forms of SLE in particular; access to alternatives such as mycophenolate mofetil (MMF), with azathioprine retaining a place of choice in maintenance, particularly in the event of a planned pregnancy, or less frequently anti-calcineurins (in renal involvement); (ii) hydroxychloroquine (HCQ): generalisation of its prescription to all SLE patients; improvement of practices to identify certain harmful drug interactions; particular attention to the reduction of effect associated with smoking; interest in measuring HCQ levels, especially to detect non-compliance but also possibly the risk of toxicity; (iii) for biologic agents: use of rituximab off-label, belimumab, and more recently anifrolumab with an evolutive positioning in the therapeutic arsenal; (iv) for corticosteroids: reduction of the doses used towards a "zero cortico" objective when possible, following awareness of the dose-dependent but also cumulative toxicity of treatment.[12]

In addition to these general optimisations, the personalisation of treatment remains an important objective. At the moment, only a few parameters are available, essentially clinical: weight (with a tendency to reduce the starting dose of cortisone to 0.5 rather than 1 mg/kg/day, favouring the administration of IV boluses),[13] skin colour (Euro-Lupus, particularly in Caucasians), type of SLE involvement (e.g. autoimmune cytopenia and rituximab), or context (e.g. azathioprine and pregnancy). Drug levels (apart from MMF area under the curve (AUC), which is not very standardised) are not used to adjust treatment dosage. The possible use of combinations of IS to limit the

doses and toxicities of the individual drugs, the optimisation of topical treatments in skin involvement (rather than increasing the dose of systemic cortisone, which is not recommended), and the introduction of complementary therapies, including non-drug therapies for the management of type 2 symptoms,[14] should be emphasised. Finally, to date, the use of biomarkers to assess disease activity and particularly to guide therapeutic choices has not yet been proven, despite encouraging results.[15-17]

Thus, while waiting for new drugs/biomarkers, the main revolution of this axis relies on the implementation of a T2T strategy guiding close control of patients until remission or low disease activity is obtained. As an international effort is ongoing to define these objectives, we will only mention the current definition used most widely (**Table 1**) and remind the reader that: (i) these objectives seems to confer similar long-term benefits;[18,19] (ii) classical biological parameters are not essential components of these definitions; and (iii) a debate on the place of physician global assessment (PGA) is ongoing,[20] with some pleading for a refinement of existing tools focusing on objective changes[21,22] that are easier to administer regularly.

ITEMS	Clinical activity	Serological activity	PGA (0-3)	Pred. mg/day	HCQ	IS and/or biologics
DORIS REMISSION on therapy	cSLEDAI =0	NA	<0.5	≤5	+	+
DORIS REMISSION off therapy	cSLEDAI =0	NA	<0.5	0	+/-*	-
LLDAS**	SLEDAI-2K ≤4		≤1	≤7.5	+	+

Table 1: T2T - definition of remission and low disease activity

HCQ: hydroxychloroquine; IS: immunosuppressants; LLDAS: lupus low disease activity state; PGA: physician global assessment; Pred: prednisolone; SLEDAI: systemic lupus erythematosus disease activity index. ***See T2U axis; ****https://calculate.mdgmedical.uk/lldas/

Finally, the consultation has an important role to play for SLE patients who are considered refractory or D2T by such an approach and we propose systematic points to consider[23] faced with such a setting, presented as the ARMADA checklist (**Table 2**). Using such an approach regularly avoids overtreatment and/or iatrogeny in some patients initially considered as refractory, but also limits therapeutic inertia and residual SLE activity in others,[32] limiting organ damage that impacts mortality.[33] Collectively, with the effort to define therapeutic aims such as remission and low disease activity, and to address potential pitfalls faced with a D2T patient, the lupologist has sufficient tools to correctly address the first axis.

ITEMS	Content	Details	Corresponding actions
A	Adherence	> 30–50% patients are not adherent	Measure blood levels of HCQ,[24] use adherence questionnaires
R	Reference	Check for possible alternative treatment, including experimental[25] /therapeutic trial participation	Use updated guidelines,[11] contact reference centres and/or participate in dedicated web multidisciplinary consultation meeting
M	Monitor	Some drugs may present pharmacodynamic variations or better responses according to specific molecular pathway activation	Measure drug AUC (MMF) Determine the presence of ADA[26] or molecular expression status[17]*
A	Await	Some drugs may have variable and delayed clinical actions	Inform patients and organise an efficient way to regularly communicate in the meantime with follow-up of surrogate biological markers when available[27]
D	Differential	Some manifestations may not be related to SLE or to current disease activity	Perform differential diagnosis when needed (infection, neoplasia, other autoimmune disease…). Identify type 2 symptoms,[28] evaluate the participation of sequelae (i.e. repeat kidney biopsy[29])
A	Attention	Various parameters may influence disease activity, requiring global or biopsychosocial attention	Identify risk factors for flares/increased disease activity: UV, tobacco,[30] current or past psychic trauma[31]

Table 2: SLE ARMADA CHECKLIST: points to consider in D2T SLE.

ADA: anti-drug antibodies; AUC: area under the curve; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; SLE: systemic lupus erythematosus.

*High or low interferon (IFN) signature (not currently recommended).

Axis n°2: Therapeutic education programs (TEPs) and screening for BASIC(s)

The importance of regular screening for toxicities of the main treatments and/or the comorbidities they promote is well supported by the literature, with, for example, data showing an excess mortality of SLE patients due to infection, excess early cardiovascular mortality (before 40 years of age) and the burden of chronic renal damage.[2,34] Screening for antimalarial-related retinal damage is also the subject of very clear recommendations,[35] even if the optimal dosage of HCQ (6.5 vs. 5 mg/kg) is still under debate.[36] Regarding corticosteroid-induced osteoporosis, recent work shows that some bone effects are mediated by the activity of SLE itself.[37]

Screening for these toxicities/ comorbidities must be part of a global management approach that also includes dietary and behavioural changes with respect to other risk factors and factors that promote relapses (UV, hormones, smoking, stress, etc.). In the long-term, patients should be encouraged to participate in educational activities, ideally in a dedicated TEP when available. We have therefore developed a basic workshop with patients entitled "BASIC(s) lupus", which allows them to review the following topics with the lupologist, in the manner of a checklist (**Table 3**) at each consultation: B (baby-contraception-fertility); A (arteries-cardiovascular risk factors-antiphospholipids); S (sunlight-skin monitoring); I (infection-vaccinations); and C (corticosteroids and associated measures). The (s) correspond to the specificities of the follow-up of specific drugs (i.e. HCQ) and/or specific organ involvement (i.e. kidneys) for which the place of preventive medical interventions to improve organ protection, although promising, warrants further studies.[44] The adoption of such a friendly tool should improve the current insufficient[1] implementation of these key items in the usual care of SLE patients, corresponding to recent European League Against Rheumatism (EULAR) quality indicators.[43]

ITEMS	Content	Details	Corresponding quality indicators§/ressources
B	Baby	Contraception Fertility preservation Pregnancy plans	QI17, QI18[38]
A	Atherosclerosis	Cardiovascular factors Antiphospholipid syndrome	QI4[39]
S	Sun	Photoprotection Dermatological screening*	QI15 Lupus Beauté Institut**
I	Infections	Vaccinations Infection prevention and management	QI16[40,41]
C	Corticosteroids	Osteoporosis Metabolic/dietary…	QI5 Cortisone-info***
(s)	Specifics	Ophthalmological (HCQ) Nephroprotective drugs	QI6, QI14[42] CRI files***

Table 3: SLE BASIC(s) CHECKLIST - regular and systematic control of comorbidities and prevention of toxicities.

CRI: Club Rhumatisme et Inflammation; § Quality indicators from the 2019 EULAR recommendations;[43] *Especially for patients on azathioprine; **https://www.youtube.com/watch?v=7k7w9QkC9FE; *** https://cortisone-info.com/; ****http://www.cri-net.com/fiches-pratiques-et-eSessions/dernieres-mises-a-jour

Axis n°3: Think to untreat (T2U) rationale and implementation

The aim is to answer, using data from the literature, a series of questions concerning the possibility, need for and modalities of therapeutic de-escalation (or de-implementation). At the moment, this is the area where the level of evidence is weakest, often based on retrospective observational cohort studies (patient selection bias) or on rare randomised studies conducted in expert centres with very close follow-up that may be far from real-life conditions, making the transposition of results difficult.

The answer to the question "Is it possible to stop one or more SLE treatments?" is clearly YES. This comes first from non-observant patients, who are not rare, and whose paradoxically satisfactory evolution, including in severe forms, can be surprising. It also comes from the experience of lupologists who have observed prolonged remission after many years of follow-up, for example after the menopause, making it possible to interrupt all treatments, sometimes including HCQ (mostly in the case of toxicity). It therefore seems that from the moment of diagnosis, it is necessary to insist on the chronic nature of the disease

while avoiding the dogmatic assertion that "lifelong treatment" will be required. In an international multicentre cohort, the rate of patients without treatment (apart from HCQ) was up to 20%.[19] Often, there is a "biological" barrier to stopping treatment (in the case of clear anti-DNA positivity and/or complement consumption), even though these abnormalities are not taken into account in the definition of remission.[8] The answer to the question "Should we stop treatment?" is also theoretically YES, since any treatment carries the potential for cumulative toxicity (infectious, cardiovascular, neoplastic, metabolic, etc.), sometimes increased by particular conditions (i.e. COVID-19 pandemic and rituximab) and even for low doses of methotrexate.[45] Another argument for stopping at least part of the SLE treatments corresponds to the "ideal prescription" strategy developed in TEPs to maintain an open therapeutic project, with a line-by-line renegotiation of the contents of the prescription, where the patient becomes aware of the utility of each drug and that compliance can lead to a reduction in the number of treatments to be taken, this motivational aspect favouring adherence.

Let us now look at what can be done for each of the four categories of SLE treatments and for which patients. For IS, the dogma of very prolonged treatment in severe forms (essentially renal) has been challenged by the recent publication of the WIN-LUPUS study.[46] In this prospective, randomised study, patients, all on HCQ, were offered (or not) to stop IS treatment after 2–3 years of maintenance treatment for a proliferative lupus nephritis and in remission for at least 1 year. The results, and this is important for the analysis of other studies of this type, can be read in two ways. First, even though the rate of renal relapses was not significantly higher in the group that stopped IS treatment (12/44 vs. 5/40), probably due to the lack of power of the study, the rate of severe lupus relapses (renal or extra-renal) was higher (14/44 vs. 5/40). Second, for 2/3 of the patients (30/44), cessation of IS treatment did not lead to a severe relapse during the 2-year follow-up. Moreover, corticosteroid consumption and systemic lupus erythematosus disease activity index (SLEDAI) were not higher in the discontinuation group. An attitude of maintaining IS in all patients would thus have led to "over-treatment" of 2/3 of the patients. This academic work therefore demonstrates that the question is no longer whether it is possible to stop treatment in certain patients, but rather how to identify patients who can be weaned. It should be noted that weaning from treatment was quite rapid in WIN-LUPUS (over 3 months), which may have disadvantaged the treatment discontinuation arm.

The available data also suggest that corticosteroid therapy can sometimes be stopped without major risk (with a fairly limited relapse rate, mainly in non-severe attacks). In the only randomised CORTICOLUP study,[47] the same double reading of the results as for WIN-LUPUS can be applied, with the same reservation about the "abruptness" of the interruption. Indeed, out of the 63 patients in the discontinuation group, 3/4 did not have any relapse and the majority of relapses were non-severe. In

another retrospective Italian study, the success rate of discontinuation was 85%, although a selection bias was noted (discontinuation was proposed in 91/148 patients).[48] Numerous studies have reported similar results,[49-52] including a recent prospective, observational study confirming the advantage of reducing steroids to <5 mg/day on lower damage accrual, especially in newly diagnosed patients.[12] Here again, the question is that of the predictive parameters of relapse and a recent meta-analysis[53] suggests that the persistence of serological activity and the absence of HCQ intake are risk factors for relapse.

Concerning HCQ, which has a special status in the management of SLE because of its mode of action, its good long-term tolerance and its pleiotropic effects (cardioprotective effects, etc.), some studies have suggested that it is possible to stop HCQ, with the notable limitation that these patients had a very long duration of lupus disease and HCQ taking.[54] More methodologically sound studies have estimated the risk of relapse when HCQ is reduced or stopped at 54% and 61% respectively, compared with continuing it.[55] Finally, data on the discontinuation of biologics are almost non-existent, but we highlight a study with belimumab, which included a very small number of patients but opens a proof of concept that suggests the possibility of initiation of therapeutic holidays.[56]

In light of all these data, it seems important not to wait to start de-escalation, at least in some of our patients. But when and how should de-escalation be initiated? On the one hand, it is obvious that de-escalation should be considered only after remission has been achieved,[8] for which the intensity (complete remission vs. lupus low disease activity state (LLDAS)) and duration are important elements. The context must also be taken into account,[57] such as an imminent pregnancy. On the other hand, it should be remembered that the best way to stop a treatment is not to start it in the first place, as for cortisone in a RITUXILUP-type protocol,[58] and that a trade-off with non-drug approaches remains a major perspective in some patients[14, 59-61].

In real-life, for a large number of patients, there is a therapeutic inertia on both sides (patients and physicians for different reasons), which has been well documented in most therapeutic areas[62] and is observed especially when remission has been slow to achieve and/or after a severe manifestation. Therefore, in the same way that the T2T concept makes it possible not to stop along the way by setting objectives concerning the control of SLE activity, with repeated re-evaluations until these objectives are reached, it seems relevant for patients who have achieved remission to introduce the mirror concept of T2U, to favour therapeutic de-escalation.

We recently proposed a tool in test phase[10] or SLE WEAN CHECKLIST which enables us to formalise the decisions shared with the patient, in order to frame and promote this new practice. Three steps of T2U are considered (**Table 4**), in this order: (i) the disease: it must be in remission, according to

a more or less strict definition, and for a period of time depending on the severity of SLE (e.g. a minimum of 2 or 3 years for lupus nephritis); (ii) the context: this is a question of evaluating the current or future factors that could destabilise the SLE (e.g. pregnancy plans) and of limiting these potential confounding factors as much as possible in the evaluation of the SLE activity (type 2 symptoms, non-adherence...); (iii) the shared choice of the modalities of discontinuation, including the objective (definitive discontinuation or therapeutic holiday, of one or several treatments) and the follow-up after discontinuation. The philosophy of this approach must be understood by the patient (i.e. that a relapse (not severe) should not be considered as a failure if therapeutic savings have been made for a significant period of time).

STEPS	Content	Details
1	Evaluate the achievement of remission or LDA	- Check for the level and duration of remission/LDA - Assess current treatment (nature and doses) - Assess the severity of the last flare - Assess SLE duration/damage
2	Mitigate potential confounders	- Assess current or anticipated risk factors for flares - Assess the presence of uncontrolled type 2 symptoms - Assess ongoing non-adherence - Assess psychosocial issues including addiction
3	Define aims and modalities	- Define the treatment to be weaned - Define if transient/definitive and partial/complete weaning - Define the modalities of weaning - Define the modalities of monitoring during/after weaning

Table 4: SLE WEAN CHECKLIST – shared decision making about therapeutic de-escalation/ withdrawal (T2U)

LDA: low disease activity; SLE: systemic lupus erythematosus.

Towards adaptive structuring of the lupologist's consultation

The lupologist's consultation distinguishes three phases of the disease, the respective durations of which depend on the patient's status at a given moment, schematically corresponding to three axes: (i) evaluation of lupus activity and tolerance of current treatments; (ii) screening for complications of the disease and/or treatments and the prevention of comorbidities/toxicities; and (iii) where possible, the initiation of therapeutic de-escalation within a shared long-term therapeutic project. Of course, in real-life these three axes are intertwined, they are ideally the object of therapeutic education during the consultation, ideally completed within a TEP with dedicated workshops

including the preparation of the consultation by the patient, and they are prioritised according to the current needs of a particular patient. However, the somewhat systematic nature of certain points to be addressed in the form of dedicated checklists should not make us forget to deal with issues that make a difference long-term (e.g. management of comorbidities).[1] These phases and corresponding tools are presented in **Figure 1**.

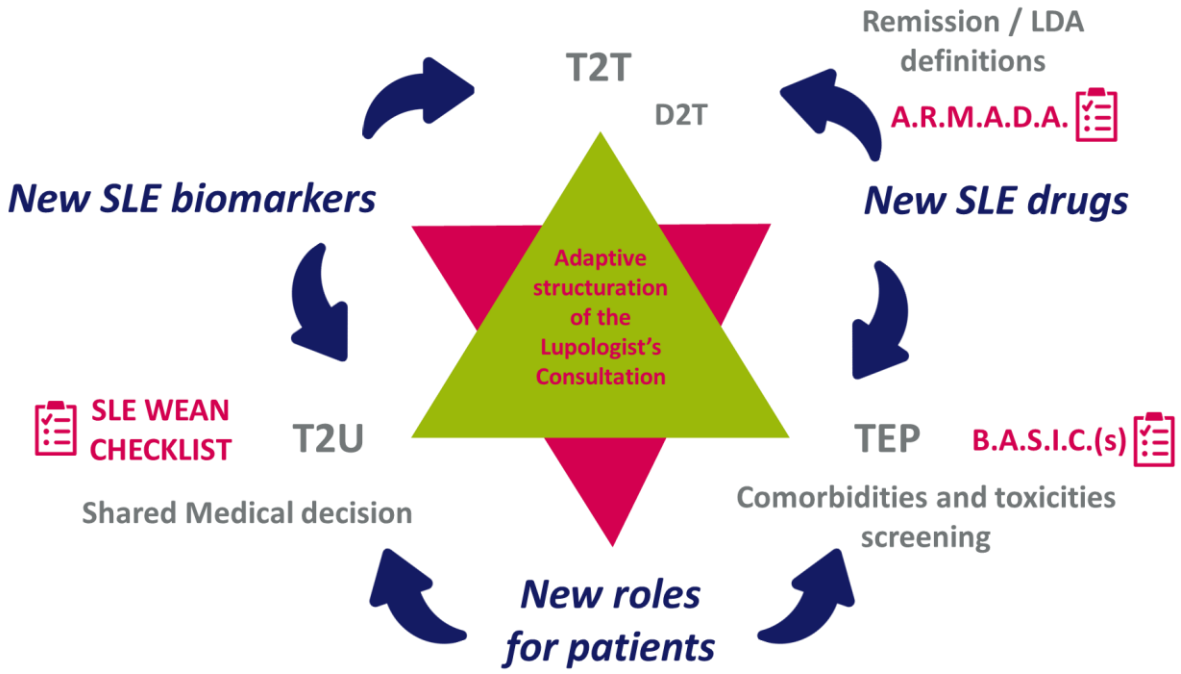

Figure 1.

T2T: treat-to-target; T2U: think to untreat; D2T: difficult to treat; LDA: low disease activity; SLE: systemic lupus erythematosus; TEP: therapeutic education programme.

As the consultation time is limited, it is clear that the first (T2T) and third (T2U) phases, artificially described in a distinct way, are perfectly complementary and therefore balance each other out according to the evolution of SLE under treatment. Nevertheless, the other disciplines that have been dealing with chronic diseases for many years teach us to be wary, on both sides of the consulting room (i.e. on the side of the doctor as well as on the side of the patient), of what is called therapeutic inertia. While this attitude may seem wise in some cases, at least for a while, it is the source of overtreatment and undesirable effects or iatrogenic sequelae that we try to actively combat by screening and prevention, but above all by setting up reasonable but active and shared therapeutic de-escalation whenever possible. The prospect of a potential discontinuation of a certain number of treatments contributes positively to the proper use of these treatments for the appropriate length of time and should prevent the high rates of poor compliance encountered in all centres. Thus we can predict that, in 2023, the SLE patient

would leave the consultation with a prescription for treatment, but with a written therapeutic plan consisting of potential deadlines and preventive actions to be put in place. The place/role of SLE patients has to evolve and include shared medical decisions as well as the self-evaluation of variable parameters of interest using validated scales (i.e. type 2, quality of life), especially between two planned consultations, with an increasing place for prescribing non-drug interventions to our patients[59-61].

Perspectives

In this paper, we hope to have stressed the potential of integrating new management paradigms in the treatment of SLE as a chronic autoimmune condition. In recent years, in addition to the creation of a network of reference centres (FAI2R) with the drafting of regularly updated PNDS[11] and the development of TEPs, it appears that there is an opportunity to transform the care pathway of lupus patients by allowing the implementation of these tools[10] within a structured consultation.[63,64] This seems to be one of the levers of the transformation of practices, and the choice of targeting the consultation itself within the care pathway of the patient living with SLE[65,66] is a prerequisite for such a transformation to be applicable whatever the specialty and the place of practice of the lupologist.

Of course, prospective randomised studies,[67,68] which will be essentially academic, are expected to guide this approach, especially T2U, to test therapeutic vacation protocols as in other therapeutic areas already put into practice in some centres (e.g. weekend interruption for HCQ), and to identify patients at risk of relapse, or even to allow for immuno-monitoring after discontinuation to anticipate these relapses. There is enough data to cautiously but surely embark on this change in our practices and to consider, in addition to remission, that the prevention of toxicities by reasonable weaning in patients living with SLE is a success long-term. An evaluation of the impact on therapeutic inertia[62] and on concrete changes in practice could be based on a collection of the items addressed corresponding to the quality indices defined by the EULAR.[43,69,70]

The structure of a consultation is one of the keys to quality of care and the doctor-patient alliance, especially in the context of a chronic disease. Ideally, this transformation would include the increased role and participation of the patients themselves.[57,71-72]

Conclusion

We propose several practical tools dedicated to the consultation of lupus patients, to define therapeutic targets (treat to target or T2T) and structure the therapeutic approach in difficult to treat patients (ARMADA checklist), to screen for and manage comorbidities and toxicities (BASICs), and to envision therapeutic de-escalation (think to untreat or T2U) in patients in remission. These tools are intended to be widely shared and used by lupus physicians, regardless of their specialty, to improve the global long-term outcome of patients with SLE.

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