


# Conceptual framework for defining disease modification in systemic lupus erythematosus: a call for formal criteria

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## ABSTRACT

Disease modification has become a well-established concept in several therapeutic areas; however, no widely accepted definition of disease modification exists for SLE. We reviewed established definitions of disease modification in other conditions and identified a meaningful effect on 'disease manifestations' (ie, signs, symptoms and patient-reported outcomes) and on 'disease outcomes' (eg, long-term remission or progression of damage) as the key principles of disease modification, indicating a positive effect on the natural course of the disease. Based on these findings and the treatment goals and outcome measures for SLE, including lupus nephritis, we suggest a definition of disease modification based on disease activity indices and organ damage outcomes, with the latter as a key anchor. A set of evaluation criteria is also suggested. Establishing a definition of disease modification in SLE will clarify which treatments can be considered disease modifying, provide an opportunity to harmonise future clinical trial outcomes and enable comparison between therapies, all of which could ultimately help to improve patient outcomes. This publication seeks to catalyse further discussion and provide a framework to develop an accepted definition of disease modification in SLE.

## INTRODUCTION

Disease modification is a well-known concept in rheumatology and other therapeutic areas.<sup>1-7</sup> However, no widely accepted definition of disease modification exists for SLE. In this article, we explore the core principles of the definitions of disease modification in other conditions, and we propose a conceptual framework for the definition of disease modification in SLE. The demonstration of a medication's capacity to modify the course of a disease would be a powerful addition to current clinical trial objectives and would ultimately help to improve patient care and clinical outcomes.

## Natural history of SLE

SLE is a chronic inflammatory autoimmune disease with fluctuating periods of relative

## Key messages

### What is already known about this subject?

► Disease modification has become a well-established concept in rheumatology and other therapeutic areas; however, in systemic lupus erythematosus (SLE), a definition of disease modification does not currently exist.

### What does this study add?

► We reviewed definitions of disease modification that exist in other diseases and identified meaningful effects on disease manifestations and outcomes as core principles of disease modification.  
► Guided by the established definitions of disease modification in other therapeutic areas along with current treatment goals and outcome measures in SLE, we propose a framework for the definition of disease modification in SLE. Organ damage prevention (or slowing), minimisation of disease activity, and avoidance of treatment-associated toxicities are the core components of successful disease modification.  
► This work, which provides criteria for a medication to be classified as a disease-modifying therapy, serves as a foundation for an exchange of ideas that could lead to further refinement of this concept in SLE.

### How might this impact on clinical practice or future developments?

► Establishing a definition of disease modification in SLE will provide a method to demonstrate the ability of a medication to modify the course of disease. This would not only be a powerful addition to clinical trial objectives but would also positively impact the care of patients.

inactivity and disease flares in most patients.<sup>8,9</sup> A loss of tolerance to ubiquitous self-antigens in SLE leads to an increase in the number of pathogenic autoantibodies, which drives inflammation and tissue injury, and the onset of clinical manifestations, which may culminate in irreversible tissue damage.<sup>10,11</sup> SLE is heterogeneous in its clinical presentations, with multiple organs being affected by



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varying degrees of severity,<sup>9 12 13</sup> which can lead to diagnostic delays and difficulties in evaluating therapeutic outcomes.<sup>10 13</sup>

Approximately 30%–50% of patients with SLE will develop organ damage within 5 years of diagnosis,<sup>14 15</sup> and 50% or more by 10 years postdiagnosis.<sup>15</sup> Patients with SLE-associated organ damage have worse health-related quality of life (HRQoL) and increased healthcare costs, morbidity and mortality versus patients with SLE who have lesser or no organ damage.<sup>16–23</sup> Damage can develop in several different organ systems, including but not limited to the ocular, musculoskeletal, neuropsychiatric and renal systems.<sup>24</sup> Patients with SLE frequently develop lupus nephritis (LN), which can progress to end-stage kidney disease (ESKD), with a 15-year risk ranging from 10% to 30% in patients with severe LN (class III, IV and V) to 44% (95% CI 32% to 56%) in patients with class IV LN.<sup>25 26</sup> Organ damage results from potentially modifiable risks such as uncontrolled disease activity/severe flares, exposure to glucocorticoids and/or immunosuppressive therapies and hypertension.<sup>27–34</sup> Other known risk factors for accelerated organ damage accrual include pre-existing organ damage, African-American race, older age at SLE diagnosis and male sex.<sup>34 35</sup>

### Treatment goals and outcomes assessments in SLE

According to the European Alliance of Associations for Rheumatology (EULAR) recommendations for SLE management, treatment goals for SLE include control of disease activity; prevention of flares and organ damage; optimisation of HRQoL; and ultimately, prolongation of life. Control of disease activity in SLE should aim to achieve remission or low disease activity and prevent flares in all organs, while minimising treatment-associated toxicities, including exposure to glucocorticoids.<sup>36</sup> In patients with LN, the goals of treatment also include preservation of kidney function and prevention of ESKD.<sup>37</sup>

The complex immunopathogenesis of SLE and heterogeneity of clinical manifestations present challenges in the assessments of outcomes and the designs of clinical trials.<sup>10</sup> According to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative, the four core areas that should be assessed in clinical trials of SLE are disease activity, organ damage, HRQoL and adverse events/medication side effects (evaluation of economic cost may also be beneficial, where applicable).<sup>38</sup> A summary of key outcome measures and instruments used in clinical trials of SLE and LN is shown in [table 1](#). We will consider the EULAR recommendations for SLE management, the OMERACT areas and established SLE assessments and instruments with the aim of selecting those most suitable for framing a definition of disease modification in SLE that can help inform prescribers and patients. Where appropriate, measures specific to LN also will be considered.

### How has disease modification been defined in other disease areas?

The concept of disease modification was first established in rheumatoid arthritis with the introduction of the term disease-modifying antirheumatic drugs in the 1980s and 1990s.<sup>39–41</sup> The various definitions of disease modification across multiple therapeutic areas identified in our literature search are summarised in online supplemental table 1.

Across all the disease areas reviewed, affecting a progressive component or the natural course of the disease is central to the definition of disease modification (online supplemental table 1). Improving the signs and symptoms of the disease is a common component within most definitions, which sits alongside modifying the natural progression of the disease but never as a standalone

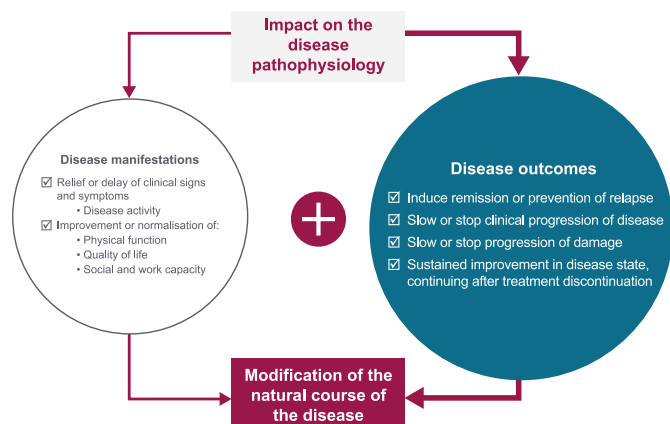
**Table 1** Key outcome measures and instruments in SLE and LN for consideration in the definition of disease modification in SLE

Type of outcome measure	Specific instrument
Disease activity indices/measures	SLEDAI, BILAG, SFI, CLASI*, uPCR†, kidney histological findings†
HRQoL measures and PROs	SF-36, FACIT-Fatigue scale, FSMC, EQ-5D, LIT, LupusQoL, LupusPRO
Global assessments	PGA, PtGA
Damage measures	SDI, eGFR decline >30%–40% and average eGFR slope reduction (>0.5–1.0 mL/min/1.73 m <sup>2</sup> per year over a 2-year to 3-year follow-up period in RCTs)†, chronicity index progression on kidney biopsy/histology†
Responder indices	SLEDAI-based and BILAG-based responder indices (SRI-4 and BICLA), different composite indices based on uPCR, eGFR and rescue medications†

\*For mucocutaneous involvement.

†For LN.

BICLA, BILAG-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; eGFR, estimated glomerular filtration rate; EQ-5D, European Quality of Life Five Dimension; FACIT, Functional Assessment of Chronic Illness Therapy; FSMC, Fatigue Scale for Motor and Cognitive Functions; HRQoL, health-related quality of life; LIT, Lupus Impact Tracker; LN, lupus nephritis; LupusPRO, Lupus Patient-Reported Outcome; LupusQoL, Lupus Quality of Life; PGA, Physician Global Assessment; PRO, patient-reported outcome; PtGA, Patient/Parent Global Assessment; RCTs, randomised controlled trials; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SF-36, Medical Outcomes Survey Short Form-36; SFI, SELENA-SLEDAI Flare Index; SLEDAI, SLE Disease Activity Index; SRI-4, SLE Responder Index-4; uPCR, urinary protein-creatinine ratio.



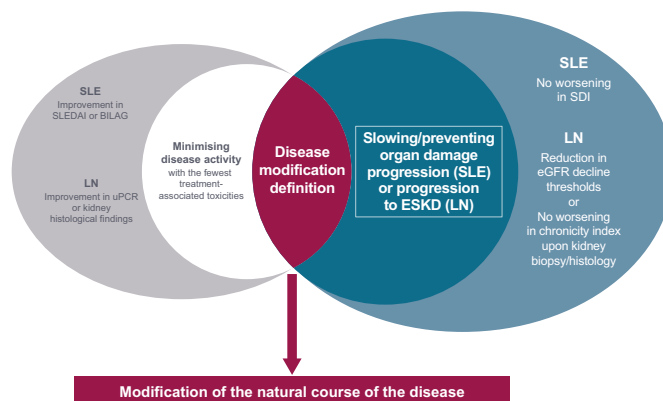
**Figure 1** Components of the definitions of disease modification from disease areas other than SLE.

component.<sup>1 7 42–44</sup> Two definitions of disease modification therapies referred to those that induce remission or prevent relapses.<sup>3 45</sup> The concept of an enduring effect was seen in the definition of disease modification in neurodegenerative disorders and respiratory diseases but not in the other disease areas.<sup>46–50</sup> Impact on the disease pathophysiology and quality of life, and evaluation of biomarkers were not consistently included as specific components of a disease modification definition across the disease areas reviewed.<sup>7 44 47 48 51 52</sup> Last, in the majority of disease areas, expert-led publications have led the way in setting out possible definitions of disease modification rather than guidance by regulatory authorities.

### What are the considerations when defining disease modification in SLE?

Drawing on the definitions from other therapeutic areas, we developed a framework for the definition of disease modification. Two key considerations were incorporated into our formulation, disease manifestations (encompassing signs and symptoms (ie, disease activity) and patient-reported outcomes (PROs)) and disease outcomes (encompassing long-term remission and slowing or stopping organ damage accumulation), and we conceptualise how both considerations may be interpreted to define a long-term meaningful change in the disease course (figure 1).

SLE disease activity is routinely assessed in clinical trials using established instruments, such as the SLE Disease Activity Index (SLEDAI)<sup>53</sup> or the British Isles Lupus Assessment Group (BILAG) Disease Activity Index,<sup>54</sup> or their modifications (table 1).<sup>55–58</sup> Although these measurements are used commonly in clinical trials, they are infrequently used in clinical practice.<sup>59 60</sup> The frequency and severity of SLE flares are indicators of global disease control and relevant in both clinical trials and in clinical practice but are not uniformly defined yet.<sup>59–62</sup> Reduction in steroid use is a key treatment goal in SLE, due to an increased understanding of the risks associated with long-term exposure.<sup>36</sup>



**Figure 2** Preliminary evaluation criteria for the working definition of disease modification in SLE and LN. BILAG, British Isles Lupus Assessment Group; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; LN, lupus nephritis; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, SLE Disease Activity Index; uPCR, urinary protein-creatinine ratio.

Recently, treat-to-target objectives in SLE, in the form of the Definitions of Remission in SLE (DORIS) criteria,<sup>63</sup> the Lupus Low Disease Activity State (LLDAS) criteria<sup>64</sup> and low disease activity criteria,<sup>65</sup> have been associated with reduced disease flares and organ damage accrual in patients with SLE.<sup>66–69</sup> Inclusion of these measures, along with flare prevention and glucocorticoid reduction, could be considered key targets in the disease manifestations component of the proposed disease modification definition framework.

The Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) is a validated measure of organ damage in SLE. However, demonstrating significant effects of an intervention on damage accrual rates requires studies that are longer than 1 year in duration.<sup>70–75</sup> In the absence of long-term trials, disease activity, a key driver of organ damage,<sup>76</sup> could serve as an interim surrogate measure of organ damage progression to determine whether an intervention is on track to achieve disease modification. Therefore, assessment of both the SDI and key drivers of organ damage should form part of a definition of disease modification in SLE with the direct assessment on organ damage via SDI as the key anchor. In addition, it is particularly important that disease activity is only considered in conjunction with *the fewest treatment-associated toxicities*, because treatments such as glucocorticoids and immunosuppressants, which reduce SLE disease activity and flares, can promote organ damage progression.<sup>29 31–33</sup>

In LN, long-term assessment of disease outcomes is focused on slowing or preventing progression to ESKD; and these outcomes can be evaluated by kidney biopsy and other clinical measures of damage, including estimated glomerular filtration rate (eGFR) slope and chronic kidney disease (CKD) staging. Histological

**Table 2** Proposed matrix for application of the SLE-specific disease modification criteria in clinical trials and clinical practice

Disease Modification definition category		Interim timepoints for assessment of disease modification <b>POTENTIAL</b> in clinical trials (vs standard therapy alone) and clinical practice (no comparison)		Disease modification <b>CONFIRMED</b>
		Outcomes year 1	Outcomes years 2–5	Outcomes year >5
Extra renal	Minimising disease activity with minimal treatment-associated toxicity <b>AND</b> Slowing/Preventing organ damage progression	<ul style="list-style-type: none"> <li>▶ Significant reduction in disease activity measured using a validated tool (ie, SELENA-SLEDAI, BILAG, SRI-4)</li> <li>▶ Significant reduction in severe flare measured using a validated tool (ie, SFI or BILAG)</li> <li>▶ Reduction in use of steroids* and/or immunosuppressants</li> </ul>	<ul style="list-style-type: none"> <li>▶ Sustained improvement in multiple organ domains/no worsening in multiple organ domains</li> <li>▶ Prevention of severe flares</li> <li>▶ Continued reduction in use of steroids* and/or immunosuppressants</li> </ul>	No change in SDI or delayed progression
Renal	Minimising disease activity with minimal treatment-associated toxicity <b>AND</b> Slowing/Preventing organ damage progression	<ul style="list-style-type: none"> <li>▶ Significant improvement in uPCR or kidney activity index via biopsy</li> <li>▶ Significant reduction in renal flare</li> <li>▶ Minimise eGFR decline (ie, &lt;30%)</li> <li>▶ Reduction in use of steroids* and/or immunosuppressants</li> </ul>	<ul style="list-style-type: none"> <li>▶ Sustained improvement in uPCR or no worsening in kidney chronicity index via biopsy</li> <li>▶ Prevention of renal flares</li> <li>▶ Minimise further decline in eGFR (ie, &lt;30%)</li> <li>▶ Continued reduction in steroids* and/or immunosuppressants</li> </ul>	No change in SDI or delayed progression

\*≤7.5 mg/day per 2019 EULAR SLE treatment guidelines and LLDAS;<sup>36 64</sup> ≤5 mg/day per DORIS remission definition.<sup>63</sup>

BILAG, British Isles Lupus Assessment Group; DORIS, Definitions Of Remission In SLE; eGFR, estimated glomerular filtration rate; EULAR, European Alliance of Associations for Rheumatology; GC, glucocorticoid; LLDAS, Lupus Low Disease Activity State; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SFI, SELENA-SLEDAI Flare Index; SLEDAI, SLE Disease Activity Index; SRI-4, SLE Responder Index-4; uPCR, urinary protein-creatinine ratio.

findings and chronicity indices determined by kidney biopsy are the gold-standard methods to assess the extent of tissue inflammation and damage.<sup>77 78</sup> Histopathology can also be predictive of renal outcome, with fibrinoid necrosis, fibrous crescents and interstitial fibrosis/tubular atrophy ≥25% predictive of progression to ESKD.<sup>79</sup> A collaborative effort between the US National Kidney Foundation, the Food and Drug Administration and the European Medicines Agency suggested an eGFR decline of >30%–40% and average eGFR slope reduction (of >0.5–1.0 mL/min/1.73 m<sup>2</sup> per year over a 2-year to 3-year follow-up period in clinical trials) as accepted surrogate end points for CKD progression.<sup>80 81</sup> Additionally, evaluating SDI at a later timepoint in patients with LN may be valuable to confirm that treatment-associated damage has not taken place.<sup>80 81</sup>

Improvement in HRQoL and PROs is an important treatment goal in SLE.<sup>36 37 82</sup> PROs can be measured using generic instruments such as the 36-item Short-Form Health Survey (SF-36), the Patient Reported Outcomes Measurement Information System item-bank (PROMIS) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, and disease-specific instruments, such as the Lupus Quality of Life (LupusQoL), the Lupus Patient-Reported Outcomes (LupusPRO) and the Lupus Impact Tracker (LIT).<sup>83</sup> HRQoL in patients with SLE is complex and can be driven by the disease itself, by

comorbid conditions associated with the disease or both; but the precise mechanism by which these processes affect HRQoL is not yet fully understood.<sup>84</sup> As such, there is a lack of consensus on the best instrument for their quantification. Given these factors, and taking into account that HRQoL and PROs measures were included in only one disease modification definition (EULAR disease modification definition for RA),<sup>43</sup> we suggest that HRQoL and PROs should be supportive elements of the disease modification definition in SLE for the time being.

Last, although definitions of disease modification in neurodegenerative disorders involve targeting the pathogenic mechanisms of the disease and biomarkers, this was not the case with the other disease areas. Indeed, in SLE there are a number of established immunological/serological biomarkers of disease, some of which (anti-double-stranded DNA immunoglobulin (Ig) G, anti-nucleosome IgG, anti-La IgG and anti-Sm IgG, interferon-inducible protein 10, monocytic chemotactic protein 1, macrophage inflammatory protein-3β and complement C3) may correlate with clinical measures of disease activity (using SLEDAI).<sup>85</sup> However, the pathophysiology of SLE is complex and heterogeneous among patients and not yet fully elucidated;<sup>85 86</sup> as such, there is no single, gold standard biomarker for assessing disease activity, rather a panel of biomarkers would likely be required. Additionally, improvement in clinical and



immunological measures do not always occur to the same extent or over the same time course. In fact, immunological responses may mirror, precede or lag behind the clinical responses. Therefore, we felt there would be limited value including pathophysiology and/or biomarkers as a mandatory component of a disease modification definition in SLE; however, it could be considered as a supportive element.

### Working definition of SLE-specific disease modification

Based on the framework developed from the definitions of disease modification in other areas, and the treatment goals and outcome measures for SLE, including LN, we suggest the following working definition of SLE disease modification:

*'Disease modification in SLE requires minimising disease activity with the fewest treatment-associated toxicities and slowing or preventing organ damage progression (or, in the case of LN, progression to ESKD).'*'

The evaluation criteria for this working definition is shown in [figure 2](#). The most definitive criteria are slowing or preventing organ damage progression in SLE as judged by no worsening in the SDI and, in LN, by showing a reduction or no worsening in key surrogates of progression to ESKD, that is, kidney histopathology or eGFR decline.

### Application of SLE-specific disease-modifying criteria

The disease modification definition for SLE could be applied to both clinical trials and clinical practice (with the notable difference that clinical trials include a comparison arm while clinical practice does not) using specific measures at year 1 to determine an impact on *minimising disease activity with the fewest treatment-associated toxicities* and at year 5 or later to evaluate *slowing or preventing organ damage progression*, with interim measures suggested for years 2–5 to determine whether an intervention is on track for achieving disease modification at the 5-year mark, as outlined in [table 2](#).

The 1-year and 5-year timeframes were chosen to assess early markers and confirmed disease modification, respectively, based on thresholds for assessment of disease activity and organ damage in clinical trials and longitudinal studies.<sup>38 80</sup> Examples of tools to be used to assess disease activity were provided, without specifying a single tool, to allow for evolution of this definition and how it can be assessed. A range of steroid thresholds are suggested to reflect the range recommended in treatment guidelines and criteria for remission and low disease activity state.<sup>36 63 64</sup>

## CONCLUSIONS

Using the established definitions of disease modification from multiple conditions as a guide and taking into consideration SLE and LN treatment goals, we have put forward a definition of disease modification in SLE, with organ damage outcomes as the key anchor.

Establishing an accepted definition of disease modification in SLE presents the opportunity for harmonising future clinical trial outcomes and will enable comparison of treatments, which could ultimately lead to improved patient care and clinical outcomes.

This article provides a preliminary definition of disease modification in SLE and will require more formal evaluation and testing before a consensus definition can be adopted. However, we anticipate that this work will provide the foundation for debates on how to achieve disease modification in SLE and the criteria that must be met for a drug to be classified as a disease-modifying therapy. As several SLE treatments may fit the disease modification criteria proposed here, the application of the criteria to current treatments is the focus of an ongoing review.

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## Supplementary material

**Supplementary Table 1.** Definitions of disease modification and/or disease modifying treatments across multiple therapeutic areas.

Condition	Definition
<b>Rheumatological disorders</b>	
<i>General rheumatological disorders</i>	<ul style="list-style-type: none"> <li>• “Disease modification is the improvement of symptoms (disease process) in conjunction with the change of the disease course (disease outcome)”[1]</li> </ul>
<i>Rheumatoid arthritis</i>	<ul style="list-style-type: none"> <li>• “A DMARD is defined as a medicine that interferes with signs and symptoms of rheumatoid arthritis, improves physical function, and inhibits progression of joint damage”[2]</li> <li>• <b>EULAR:</b> “The concept of ‘disease modification’ comprises a combination of relief of signs and symptoms; improvement or normalization of physical function, quality of life and social and work capacity; and most characteristically the inhibition of occurrence of progression of structural damage to cartilage and bone”[3]</li> <li>• <b>ACR:</b> “Agents that apparently alter the course and progression of rheumatoid arthritis, as opposed to more rapidly acting substances that suppress inflammation and decrease pain, but do not prevent cartilage or bone erosion or progressive disability”[4]</li> </ul>
<i>Systemic sclerosis</i>	<ul style="list-style-type: none"> <li>• “Ideal DMT should halt the progression of the disease and hopefully induce remission, and preferably also reverse some of the major organ complications... It is reasonable to expect a DMT to stabilize organ function without any further worsening of other domains”[5]</li> </ul>
<b>Neurodegenerative disorders</b>	
<i>General neurodegenerative disorders</i>	<ul style="list-style-type: none"> <li>• “A disease-modifying therapy is an intervention that produces an enduring change in the trajectory of clinical decline of a neurodegenerative disorder by impacting the disease processes leading to nerve cell death”[6]</li> <li>• <b>EMA:</b> “For regulatory purposes, a disease modifying effect will be considered when a pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by improvement in clinical signs and symptoms of the dementing condition”[7]</li> </ul>
<i>Alzheimer’s disease</i>	<ul style="list-style-type: none"> <li>• “Disease modification can be defined as treatments or interventions that affect the underlying pathophysiology of the disease and have a beneficial outcome on the course of Alzheimer’s disease”[8]</li> <li>• “A disease-modifying therapy is as an intervention that produces an enduring change in the clinical progression of Alzheimer’s disease by interfering in the underlying pathophysiological mechanisms of the</li> </ul>



	<p>disease process that lead to cell death”[9]</p> <ul style="list-style-type: none"> <li>• <b>EMA:</b> “A medicinal product can be considered to be disease modifying when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes. This can be demonstrated by results that show slowing in the rate of decline of clinical signs and symptoms and when these results are linked to a significant effect on adequately validated biomarkers. Such biomarkers should reflect key pathophysiological aspects of the underlying disease process based on a plausible disease model. The choice of biomarker as well as the type of analysis is left open, although more weight will be given to those biomarkers showing not only target engagement, but also an effect on the downstream disease mechanisms”[10]</li> <li>• <b>FDA:</b> “Permanently altering the course of Alzheimer’s disease through a direct effect on the underlying disease pathophysiology; the effect persists in the absence of continued exposure to the drug”[11]</li> <li>• <b>PMDA:</b> “Medical agents that delay neurodegeneration and neuronal cell death by acting on the pathological mechanism of Alzheimer’s disease and, as a result, inhibit the progression of clinical symptoms”[12]</li> </ul>
<i>Epilepsy</i>	<ul style="list-style-type: none"> <li>• “According to the definition of epileptogenesis, ‘disease modification’ refers to every clinically relevant therapeutic outcome which does not necessarily prevent epilepsy onset but significantly improves the disease course by reducing seizure burden and/or decreases concomitant comorbidities”[13]</li> </ul>
<i>Multiple sclerosis</i>	<ul style="list-style-type: none"> <li>• Disease-modifying therapies are “drugs targeted to prevent relapses of the disease, and consequently, progression of disability”[14]</li> </ul>
<i>Parkinson’s disease</i>	<ul style="list-style-type: none"> <li>• “A disease-modifying therapy... slows or stops disease progression”[15]</li> </ul>
<b>Respiratory diseases</b>	
<i>COPD</i>	<ul style="list-style-type: none"> <li>• “An improvement in, or stabilization of, structural or functional parameters as a result of reduction in the rate of progression of these parameters which occurs whilst an intervention is applied and may persist even if the intervention is withdrawn”[16]</li> </ul>
<i>Emphysema</i>	<ul style="list-style-type: none"> <li>• “Disease modification is a sustained improvement in disease state following therapeutic intervention that persists when therapy is discontinued”[17]</li> </ul>

ACR, American College of Rheumatology; COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drug; DMT, disease-modifying therapy; EMA; European Medicines Agency; EULAR, European Alliance of Associations for Rheumatology; FDA, US Food and Drug Administration; PMDA, Japanese Pharmaceuticals and Medical Devices Agency

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