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Target Therapy in SLE

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ABSTRACT

The intention of this paper is to review actual developments in target therapy in SLE. Target therapy includes both the objective of intervention and the aim of treatment. The objective should be linked to the pathophysiologic process of SLE; the aim has to be in any case an improved outcome.

The current therapeutic in SLE is guided mostly by secondary prevention. In SLE, besides a BASIC concept with antimalarials, bone and sun protection, vaccination and cardiovascular risk minimising, treatment waits for new manifestations to be started to prevent secondarily damage. With the new treatment target remission, treatment should aim at ensuring long-term survival, preventing organ damage and optimizing health-related quality-of-life by controlling disease activity and minimising comorbidities and drug toxicity. First examples show that some patients are in remission and that those patients have a better outcome. But for treat-to-target a strategy needs to be developed that needs to be evaluated.

During the last decades survival of patients with systemic lupus erythematosus (SLE) improved significantly [1], although new medications were not licensed despite belimumab. But SLE patients are still facing an increased mortality rate and suffering from a meaningful burden of their now chronic disease [2] [3],. Evidence based recommendations were developed to further improve the outcome SLE patients, which are defining the standard of care in SLE today [4–8]. Their wide spread implementation will certainly further reduce the burden of SLE, but new therapeutic options and more individualized interventions are needed to change the outcome importantly.

Target therapy is this context includes both the objective of intervention and the aim of treatment. The objective should be linked to the pathophysiologic process of SLE and it would be a surprise, if in the heterogeneity of SLE one fits for all patients and disease states. The aim has to be in any case an improved outcome or finally healing, and in-between various interim aims based on clinical or pathophysiologic parameters need to be established and implemented. The targeted components of therapy, objective and aim, are linked to each other and therefore their development has to take that into account. The intention of this paper is to review actual developments in target therapy in SLE focusing on this interaction as any objective can only be evaluated by predefined aims.

Pathophysiology SLE = Targets.

In SLE, the number of probably pathophysiologically based targets is great, but until now no clear candidate cell or molecule for intervention was fixed. Interventions are mostly focused on B-cells directly (e.g. rituximab, epratuzumab) or B-cell growth factors (e.g. belimumab, atacicept), cell-cell interactions (e.g. abatacept), type 1 interferons (e.g. sifalimumab) or their receptors (e.g. anifrolumab), or cytokines like TNF, Il 2 or Il 10 and the elimination of autoantibodies [9]. Most results were disappointing, but the promising and successful trials showed that focusing on subsets of patients may be beneficial, e.g. ANA positivity and probably high disease activity in belimumab trials and IFN signature in anifrolumab [10–12]. And the challenge will be now to evaluate the optimal conditions for every new tested target, as these conditions seem to be different from drug to drug.

1. Current therapeutic concept

The current therapeutic in SLE is guided mostly by secondary prevention as aim, targets to reach are only nebulously set. According to present guidelines all patients should treated based on the BASIC concept [13] (Table 1). Every patient should be take antimalarials, which are proven to be flare preventive, protecting also against organ damage and new manifestations as well as displaying several other beneficial effects in SLE [14]. UV (sun) protection is recommended not only to prevent skin rashes, but also systemic exacerbations. And because infections and cardiovascular complications are the major causes of increased mortality, vaccinations (immunisation protection) and minimization of common cardiovascular risk factors, e.g. smoking, hypertension, should be addressed from disease onset. Due to high risk of osteoporosis in SLE every patient should treated at least with vitamin D supplementation for bone protection.

On top of this BASIC concept, every patient should be monitored at

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Table 1
BASIC concept in care of SLE patients [13].

	Measures	Indicated in
Bone protection	Vitamin D (20.000 IU/Week)	All (low 25OH-VitD)
Antimalarias	Hydroxychloroquine (200 mg/d)	All (no contraindication)
Sun protection	SPF50, clothing	All with UV-sensitivity
Immunisation protection	Standard & Influenza, Pneumococci	All
Cardiovascular risk	Risk factor evaluation & modification	All

each visit for new manifestations, especially for new major organ involvement. Early detection and early treatment reduce the risk of damage. Depending on disease expression, additional immunosuppressive treatments are mandatory as also complementary management [15]. This therapy is then adapted over time mostly driven by the response of the involved organ. But clear recommendations for reducing immunosuppression are missing, as also clear targets of the intervention. Only for lupus nephritis a validated target is available with a proteinuria of < 700 mg/d [15], for all other manifestations therapeutic intervention is mostly guided by personal experiences. Especially, despite enormous investment biomarkers are still missing as guidance of therapy.

Lupus therapy therefore follows somehow the paradox of "Achilles and the Turtle", where the fast Achilles cannot reach the slow turtle: every time when he reaches the point where the turtle was when he started the turtle moved away. In SLE, beside BASIC, treatment waits for new manifestations to be started to prevent secondarily damage. A typical example is the diagnosis of anti-phospholipid syndrome, which can earliest be diagnosed when manifestation happened like stroke, abortion or venous thrombosis. The same is true for lupus nephritis or other manifestations, so that treatment is initiated not till then the pathophysiological process already caused organ inflammation or even damage.

2. Clinical process – target disease activity

The driving force of the pathophysiologic process is labelled "disease activity" and is mostly defined by the disease expression as flares and organ manifestations (Fig. 1, left side). It is somehow based on the genetic background with obvious differences between races [16–18], moreover, epigenetic modifications are influencing this processes as also environmental factors, e.g. smoking or infections, and hopefully our immunosuppressive medications. Disease activity is somehow captured by the various activity instruments [19], and uncontrolled disease activity as also medications lead to accelerated damage and increased mortality rate [20].

2.1. Target remission

Despite its imprecise definition, disease activity seems the best target for therapy in SLE, like DAS 28, CDAI or SDAI in rheumatoid arthritis (RA), where the concept of treat to target is widely accepted. In RA the target is remission, a disease state that does not cause further damage [21]. For SLE, a group around Ron van Vollenhoven started a process to define remission as a target: Treatment of SLE should aim at ensuring long-term survival, preventing organ damage and optimizing health-related quality-of-life by controlling disease activity and minimising comorbidities and drug toxicity [22]. In real life, rheumatologists and nephrologists believe that most of their lupus patients are in remission [23]. But these patients still have a significant disease expression despite a nearly similar treatment in respect to patients not considered in remission. The DORIS group developed several definitions of remission [24]. In parallel, the "lupus low disease activity state" LLDAS was developed and validated by a group around Eric Morand [25].

Several groups showed that being in the state of remission or LLDAS is associated with a favourable outcome. The Asian-Pacific registry documented that patients with more than half time in LLDAS, patients suffered from less flares and less organ manifestations and consequently needed less harmful medications [25]. Andrea Doria and his group analysed their cohort and found only 7% patients in complete remission without steroids [26], but this group of patients has the greatest chance for long-term remission which is associate with improved outcome [27,28]. They also detected vasculitis and anti-phospholipid syndrome as disease activity independent predictors of outcome [29].

In the GLADEL population remission off therapy was less frequent and it could be shown that remission is better predicting "no severe damage" than LLDAS [30]. In M. Petri's cohort a 50% time in either remission or LLDAS led to a nearly 50% reduction in damage [31], in keeping with results from Padua cohort, indicating a 2 years remission as the shortest period protecting against damage. In conclusion, all these data exhibit that being in remission or LLDAS favours a better outcome. But as indicated by analyses from the Amsterdam cohort and other results, the targets are less often reached by patients with the

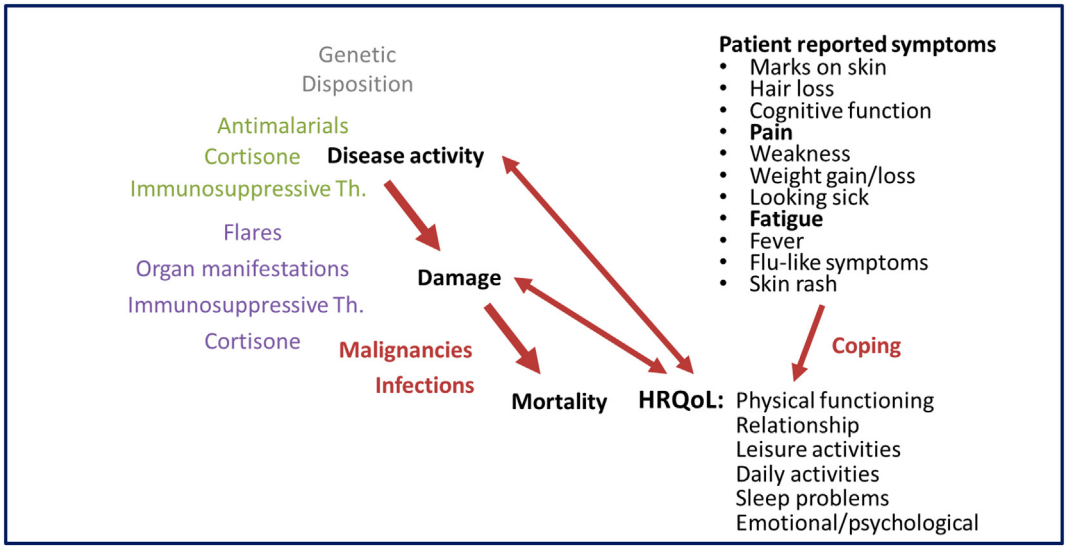

Fig. 1. Elements for strategies in SLE [16,36–38].

history of major organ involvement [32], so the group of patients in remission or LLDAS is mostly a selection of milder ill patients. Post-hoc analyses from clinical trials using LLDAS showed at least low disease activity could be a target to treat [33].

According to the consensus of experts, remission has at least 3 domains: disease activity, serology and therapy [34]. LLDAS is based on disease activity and therapy [35]. Both concepts refer for disease activity to SLEDAI (or other validated disease activity scores), LLDAS uses in addition physician global assessment (PGA), which was also evaluated in the context of remission [34], and in response criteria like SRI [34]. As indicated e.g. by the natural documented remission rate in daily care, PGA bears the risk of high subjectivity and less inter-observer agreement, and its use is mostly based on the perceived insufficiency of the validated scores to capture disease activity. But as disease activity is perceived as the most relevant domain for outcome, a more precise instrument is needed as target for therapy instead of weakening the existing ones by addition of PGA. Even experts do not agree significantly in judging response in SLE: 7 points in SLEDAI are needed for 70% agreement in improvement [35]. Despite intensive research, actually available serology is of no benefit in evaluating disease activity. This domain is more a research tool than a predictable parameter.

In SLE, also the optimal target glucocorticoid (GC) dosage needs also be defined; remission and LLDAS use actually different definitions of upper limit in daily dose [34,35]. Clinical care is often characterized by fight about milligrams, and GCs are more easily increased than reduced. As the benefit of long-term low dose GCs is not proven by evidence and harm is indicated [20], a more practicable point of view may be to aim for complete GC tapering to zero every time when GC are started. If no GC is the clear target, the door will also be opened for new drugs that fill the gap.

In RA, analyses of the best predictive parameters came up with a patient reported outcome (PRO) as important independent factor (Fig.1, right side). In SLE, PROs are ignored as part of target therapy, because experts believe that fatigue, pain or physical activity are not relevant for outcome or at least not validly reflecting a clear defined pathophysiological process. But as reimbursement in general is mainly based on health related quality of life, PROs should be at least part of the further evaluation of remission in SLE, either for defining remission or as outcome.

2.2. Strategy

Finally after defining a general accepted aim, the greatest challenge in target therapy is to agree on the best way to reach the aim. In SLE, such a strategy is until not recommended in guidelines as remission or LLDAS are not yet generally accepted as aims for some or all SLE patients. Strategies in contexts e.g. of economy integrate every variable that may influence the option to reach the aim. Until now only disease activity and therapy are set, but they only represent a part of the aim in SLE. Obviously disease activity and medications are also relevant parameters to be considered when initiating and performing a target therapy, as also the type of previous fluctuations of disease activity as well as its responses to earlier interventions. Other known important values are organ manifestations and their severity of activity including already existing damage; these values are indicators of the highly variable disease process in SLE. Likewise obvious is the importance of comorbidities, infections and the risk of acquiring infections as these factors may limit therapeutic options and in addition may limit the capacity to recover.

It is also well known that sex, ethnicity and age at onset are variables that define in some way the picture of SLE and the response to therapy; therefore they also should be ingredients of a strategic approach like target therapy in SLE. In addition, any biomarker that is known to indicate somehow the pathophysiologic process in SLE, e.g. complement deficiency, should shape the strategy to reach the target. A difficult to capture, but important factor is also compliance.

In clinical trials of SLE, just disease activity and actual medications are used as inclusion criteria; some comorbidities or organs manifestations may be relevant as exclusion criteria. Until now, those trials are not strategic at all despite a defined primary objective. For evaluating the strategic approach to target therapy, start could be a broad and best combined retrospective evaluation of all these know factors influencing strategy in SLE for outcomes, especially therapeutic response. Such a process can be best based on registry data and may include explorative big data concepts.

Finally we need to overcome the “Achilles and the Tortoise” (Zeno, 5th century BCE) in treating SLE; we need to pass by our current responsive strategy first by controlling and documenting disease activity and health related quality of life in our patient at every visit. This should give us a feeling where we need to intervene more actively. The next step may be to aim for LLDAS in every patient and thereby evaluate how the individual factors influence our strategic options. The final step to target therapy should finally be guided by the specific pathophysiologic process of the individual SLE patient and aiming for remission. Then definition of remission needs also to be based on the individual process and the strategy does not wait for the turtle to move.

At this stage of precise medicine pathophysiology related targets can be easily evaluated, because the specific interventions can be evaluated at the target level. This will be a realistic platform for basket trials in SLE and change completely the direction of analysis.

Actually target therapy means a new, based on in vitro data pathophysiologically relevant target will be applied in phase II clinical trials in SLE while a clinical outcome will be used for primary analysis. Secondly, a possible interaction between changes in target function by the intervention and this clinical outcome will be screened. In most cases, this read out is based on secondary signals (surrogates) as follow up out of the drug function which increases the risk of misleading interpretations. But we still hope to identify the most important targets with this strategy ignoring nearly all factors known to influence the response.

Future target therapy needs to be guided by the target not in abstract but with a read out directly on target function in patients with pathologic reactions of this target.

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