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When should targeted therapies be used in the treatment of lupus nephritis: Early in the disease course or in refractory patients?

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ABSTRACT

Although the prognosis of lupus nephritis (LN) has improved over the last few decades, 5–20% of patients still progress to kidney failure. Hence, there is an unmet need to improve the management of LN. Two novel drugs, belimumab and voclosporin, have been recently approved for LN and obinutuzumab is in the late stage of development. In randomised controlled trials (RCTs), all these drugs, added to the standard-of-care, were more effective than standard-of-care alone in achieving renal response. Now the question is: should these new drugs be used early in the disease course or just in refractory patients? The main reasons supporting the early use are based on the RCTs that demonstrated benefits when combinatory regimen was initiated early in incident and relapsing patients leading to a higher proportion of patients to achieve renal response, hence reducing nephron loss and the risk of kidney failure. The main reasons supporting the use of the combinatory regimens primarily in relapsing/refractory patients acknowledge that many patients responded well even without add-on medications, allowing a more economic use of innovative and costly drugs. However, good predictors of renal response to standard-of-care are lacking and, thus, the decision of adding new treatments early or just in refractory or relapsing patients has to consider drug access, risks of over or undertreatment, and preservation of kidney function in high-risk individuals.

1. Introduction

Systemic lupus erythematous (SLE) is a complex autoimmune disease characterized by a relapsing-remitting course [1] and a wide spectrum of clinical features: from mild [2] to severe manifestations such as lupus nephritis (LN) [3] and central nervous system involvement [4]. A number of environmental factors can potentially trigger the onset of disease [5] leading to the production of autoantibodies, which can eventually be responsible for tissue inflammation and damage [6–8]. LN occurs in approximately 50–60% of patients [3,9,10] and is one of the most serious manifestations of SLE since it is associated with a significant morbidity, mortality [11] and worsening of health-related quality of life [12]. In a study on annual direct medical cost of active SLE, carried out in five European countries, the mean annual direct medical cost of severe manifestations was almost twice that of non-severe manifestations and LN was one of the most significant independent predictors of these costs [13]. The category of health resource use, which mostly affects the direct medical cost of lupus, is the treatment [13]. Thus, the management of LN is a real challenge both in terms of patient prognosis and economic burden. LN treatment has evolved over time thanks to the introduction of new drugs [14]. Among the most important advances of the last decade is the widespread use of mycophenolate mofetil (MMF), Rituximab (RTX) [15], despite the failure of LUNAR trials, and tacrolimus. Thanks to these drugs, there is now the attempt to use a lower dose of glucocorticoids than in the past with the aim of dampening the glucocorticoid-related damage [16]. An Italian multicentre study [17], carried out in 499 patients with biopsy proved LN followed up for about 50 years, showed the prognosis of LN has progressively improved in terms of survival without a decrease of glomerular filtration rate (GFR) below 60 mL/min per 1.73 m^2 or without kidney failure. Nevertheless, there are some shortcomings in the current treatment of LN: a consistent proportion of patients (about 30%) do not

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achieve either complete renal response (CRR) or partial renal response (PRR) [18,19]. Additionally, consistent proportions of patients (40–50%) who achieve CRR or PRR develop a relapse of LN during follow-up [19,20] and from 5 to 20% of all patients with LN develop kidney failure within 10 years of LN diagnosis [17,21] Another emerging aspect [22], is that the failure to achieve the EULAR/ERA-EDTA response at one year is the most significant independent predictor of poor long term kidney outcome suggesting that kidney response should be achieved as soon as possible. Very recently, two new drugs were approved for LN. The first is Belimumab, a monoclonal antibody that selectively binds and inhibits B lymphocyte stimulator (BLyS), a survival factor for B cells, already approved for active non-renal SLE in 2011. The effectiveness of Belimumab in patients with LN has recently been confirmed in a large real-world study [23]. The second is Voclosporin, a new calcineurin inhibitor, an analogue of cyclosporine with an increase in vitro potency compared to cyclosporin. In addition, Obinutuzumab, a human anti-CD20 monoclonal antibody, more effective than Rituximab in depleting B cells, is in a late stage of development. All these new drugs have been used as add on therapy over the standard of care. Now the question is: when should these new drugs be used in the treatment of lupus nephritis? In this review article we discuss two opposite views: "early in disease course", presented by Ioannis Parodis, or "in refractory patients", presented by Hans-Joachim Anders.

2. Early in the disease course

Each flare of LN leads to substantial nephron loss, in some cases, evolving to ESKD [9]; thus, LN should always be considered a severe condition, and be treated as such. The current sequential treatment paradigm comprises an initial phase of LN treatment aiming at disease control, followed by a remission maintenance phase. Standard therapy for the initial phase comprises methylprednisolone at a total dose of 0.5–3 g followed by oral predniso(*lo*)ne at a dose of 0.3–0.5 mg/kg/day tapered to $\leq$7.5 mg/day within 3–6 months, along with oral mycophenolate mofetil (MMF) at a dose of 2–3 g/day or low-dose intravenous cyclophosphamide CYC given as infusions of 500 mg every second week for a total of six infusions (three months). The remission maintenance phase consists of either MMF or azathioprine (AZA). The total treatment period should not be shorter than three years [24]. Hydroxychloroquine should be given to all patients unless contraindicated [25]. Calcineurin inhibitors (CNI) are mainly used in membranous LN as an add-on to enhance reductions in proteinuria and improve treatment outcomes. In refractory cases, treatment may be intensified by means of therapy switch, addition of a CNI, or RTX.

With current treatment strategies, CRR is only achieved in 20–30% of the patients [26,27], relapses are common [9,28], and 5–20% of LN patients develop ESKD within 10 years [29–31], irrespective of the treatment regimen they are given. Thus, there exists an urgent need for improvement of the therapeutic strategies for LN. Nevertheless, along the implementation of treat-to-target approaches, a paradigm shift is being witnessed from the current sequential to combinatory and personalised regimens.

The unknown target of LN therapy poses challenges. Evidence from the Euro-Lupus (30) and MAINTAIN [32] Nephritis Trials suggests that early reductions in proteinuria are coupled with a favourable long-term outcome, and a cut-off of 0.7–0.8 g/day at one year of therapy is the best predictor to date of a favourable outcome seven years after the LN onset [33–35]. However, best to date does not mean good enough; in this respect, a series of studies have shown that clinical (mainly based on proteinuria) and histological (based on actual inflammatory activity in repeat biopsies) treatment outcomes are discordant [36–38], for reasons explained in the second part of the article.

2.1. Combining drugs to treat LN

The current treatment paradigm was challenged in two recent randomised phase III clinical trials, that of belimumab and that of voclosporin, both suggesting combinatory regimens with an add-on targeted agent on top of standard immunosuppression with MMF or CYC.

2.1.1. The prospect of belimumab in LN

SLE is considered a B cell-driven disease, with the B cell cytokine B cell activating factor belonging to the TNF family (BAFF; also known as B lymphocyte stimulator, BLyS) playing key roles in pathogenesis, with importance also shown in the context of LN [39]. Belimumab is a blocker of the soluble counterpart of BAFF, with proven efficacy in treating SLE across several phase III randomised clinical trials [40], which however excluded patients with severe active LN. Later, the LN-specific phase III BLISS-LN trial [41] randomised 448 patients with a biopsy-proven LN class III–V to intravenous belimumab or placebo as add-on to oral glucocorticoids along with intravenous CYC followed by oral AZA, or oral MMF. The trial met its primary endpoint, which was the composite Primary Efficacy Renal Response (PERR) at week 104; PERR was achieved by 43% of the patients in the belimumab arm and 32% of the patients in the placebo arm [41].

Among drawbacks, it is worth mentioning that the benefit conferred from belimumab was only documented in patients who received belimumab on top of MMF and not in patients who received it on top of CYC/AZA, and only in non-black patients [41]. An explanation for the former may be that patients in the CYC/AZA arm had a more severe disease, supported by the higher proteinuria levels, lower eGFR, lower complement levels, and longer SLE disease duration at baseline, while for the latter an explanation may lie along the fact that black populations are known to have a more severe LN course (9). Moreover, it is important to mention previous reports of de novo LN cases during belimumab therapy [42], illustrating that the same size may not fit them all.

2.1.2. The introduction of voclosporin

CNIs have long been used with favourable effects in the treatment of LN, especially in Asian LN populations [43]. Voclosporin is a modern analogue to cyclosporin with enhanced inhibitory potency against calcineurin and a quicker elimination of metabolites, posing fewer monitoring challenges compared with cyclosporin and tacrolimus. After the promising phase II AURA-LV trial [44], the phase III AURORA trial included 357 patients with LN class III–V who were randomised to oral voclosporin (23.7 mg twice a day) or placebo on top of MMF and glucocorticoids. After 52 weeks of therapy, 41% of the patients in the voclosporin arm met the complete renal response (CRR) criteria of the trial versus 23% in the placebo arm [45]. Among the drawbacks, the long-term toxicity of voclosporin is yet to be determined, as are its effects on extra-renal disease activity and prevention of renal relapses. In fact, whether the potency of voclosporin in stabilising the podocytes overestimated its effect on suppressing inflammation has been a matter of debate. To address these questions, repeat biopsy data would be needed.

2.1.3. The prospect of obinutuzumab and anifrolumab

In the same spirit, the ongoing phase III trials of obinutuzumab and anifrolumab in LN use combinatory regimens. Obinutuzumab is a new generation anti-CD20 monoclonal antibody and was tested for LN in the phase II NOBILITY trial [46], the heartening results of which along with an adequate safety profile warranted the ongoing phase III REGENCY trial (NCT04221477). In both trials, obinutuzumab challenges placebo as an add-on to standard immunosuppression, and is given at baseline and after six months of treatment. Anifrolumab is a human monoclonal antibody against the type I interferon receptor (IFNAR), that was recently approved for active extra-renal SLE after completion of two phase III trials, i.e., the TULIP-1 [47] and TULIP-2 [48] trials, which however excluded active LN. The subsequent phase II TULIP-LN trial included 145 patients with biopsy-ascertained LN, who were randomised to anifrolumab basic regimen, anifrolumab intensified regimen,

or placebo every fourth week on top of glucocorticoids and MMF [49]. While the trial did not meet its primary endpoint, the intensified regimen of anifrolumab was numerically superior to placebo in several clinical outcomes, including CRR at week 52 (46% versus 31%). This justified the subsequent phase III trial, again testing anifrolumab as an add-on to standard immunosuppression from the beginning of the trial intervention. Similar combinatory approaches have been followed in more recent trials, e.g., that of add-on secukinumab, an interleukin (IL)-17A inhibitor (NCT04181762), which however was terminated prematurely.

2.2. The problem of which drug to choose

The treatment landscape in LN is changing with more available drugs, and towards a shift from the current paradigm of sequential therapy to combinatory regimens, with a targeted add-on combined with standard immunosuppression from the beginning of LN treatment. This also changes the challenge from unavailability of drugs to how to wisely choose the right drug for the right patient. Among current options, one would anticipate that patients with LN who also have extra-renal manifestations will likely be prioritised for belimumab rather than voclosporin, whereas high-grade proteinuria would probably prompt a choice of voclosporin. Needless to mention, biomarkers that reflect kidney pathology are eagerly needed to guide decision-making.

2.3. Why use targeted therapies early and not wait?

With belimumab and voclosporin having enriched the treatment armamentarium for LN and with more treatments being awaited in the near future, a debate about the right time to use those new treatments has emerged, i.e., early at the time of LN diagnosis or after an initial treatment failure.

While drug costs will certainly impede physicians adding the targeted agent already from the beginning, one could make strong arguments for prompt use of combinatory regimens. Firstly, the data on the efficacy of belimumab and voclosporin for treating LN come from clinical trials which were designed to test the combinatory regimens from the beginning of LN treatment. Thus, there is currently no evidence-based incentive for a "wait-and-see" approach. Secondly, even though the added effect of addition of belimumab or voclosporin was not dramatic, in fact only increasing the proportions of CRR attainment from ~30% with standard immunosuppression alone to slightly >45% at best with the combinatory regimens, it is fair to claim that in this patient population, mainly consisting of young women during their fertile years of age, preservation of the renal function for even a few more patients than those who would be successfully treated with MMF or CYC alone should be considered of significant importance. Thirdly, while costs may be an issue in some cases/contexts, indirect costs from progression to ESKD also constitute an important burden to societies.

In summary, it is evidence-based, patient-centric, and of reasonable cost burden to treat early, aiming at sparing nephrons at the greatest possible extent, thus helping prolong the kidney lifespan in this young population of patients.

3. In refractory patients

3.1. Lupus nephritis is just another form of autoimmune glomerulonephritis but more complicated

LN is one of many forms of autoimmune GN, but it differs from most other forms by in terms of the number of autoantigens (Table 1) [50]. While most autoimmune GNs develop from autoimmunity directed against a single autoantigen, SLE is characterized by loss of tolerance against numerous chromatin elements as well as again other autoantigens [51]. This implies that treatment of SLE and LN must sufficiently suppress a much larger number of autoreactive lymphocyte clones as compared to other autoimmune diseases, albeit still less compared to recipients of an organ transplant (Fig. 1). Therefore, LN clearly requires more immunosuppressive therapy compared to a simple autoimmune disease such as ANCA vasculitis or primary membranous glomerulonephritis with only few clones to control. Which of the autoreactive clones produces circulating nephrotoxic agent(s) is unclear, therefore it remains difficult to monitor immunological activity in LN as compared to autoimmune GNs with a single, well-defined, nephrotoxic autoantibody [9].

3.2. Lupus nephritis lacks a reliable marker of immunological activity

This lack of a reliable biomarker of immunological activity of SLE is the main source of the persistent confusion how to properly treat LN as it remains difficult to assess response to treatment and residual disease activity [52]. Proteinuria is used instead [24,53], although proteinuria is only loosely related to the mechanism-of-action of most immunosuppressive drugs and although rebiopsy studies have shown that proteinuria is an unreliable marker of the immunological activity of LN [34,54,55]. That is why the question of whether to use targeted therapies in refractory LN, fails at the point of the definition of refractory disease [56].

Table 1
Lupus nephritis is one of many forms of auto/−alloimmune glomerulonephritis.

	Autoreactive lymphocyte clones directed against:	Circulating nephrotoxic agent	Biomarker of immunological activity	Predominant lesion pattern at kidney biopsy
Single epitope/ antigen	NC1-collagen4-α chain	Anti-Col4a IgG	Anti-GBM IgG titre	Crescentic GN with linear IgG along GBM
	Gd IgA1	Anti-Gd IgA1	Not available	Proliferative GN
	IgG	Cryoglobulins	Cyroglobulins	Proliferative GN
	Proteinase-3	PR3 ANCA	PR3 ANCA	Crescentic GN
	Myeloperoxidase	MPO ANCA	MPO ANCA	Crescentic GN
	PLA_2R: CysR, FNII, CTLD	Anti-PLA_2R IgG	Anti-PLA_2R IgG titre	Membranous GN
	TSHD7A: TSD1	Anti-TSHD7A-IgG	Anti-TSHD7A-IgG titre	Membranous GN
	NELL-1	Anti-NELL-1 IgG	Not available	Membranous GN
	Semaphorin 3B	Anti-SEM3B IgG	Not available	Membranous GN
	Procadherin-7	Anti-PCDH7 IgG	Not available	Membranous GN
	HTRA1	Anti-HTRA1 IgG	Not available	Membranous GN
	Contactin-1	Anti-contactin IgG	Not available	Membranous GN
	Netrin G1	Anti-netrin 1 IgG	Not available	Membranous GN
Numerous antigens	Nuclear antigens (100 s)	Numerous autoantibodies	Anti-dsDNA IgG titre loosely correlated	Proliferative GN or Crescentic GN or Membranous GN
	Donor organ-related (1000s)	Donor-specific alloantibodies	Donor-specific alloantibodies	Transplant glomerulopathy

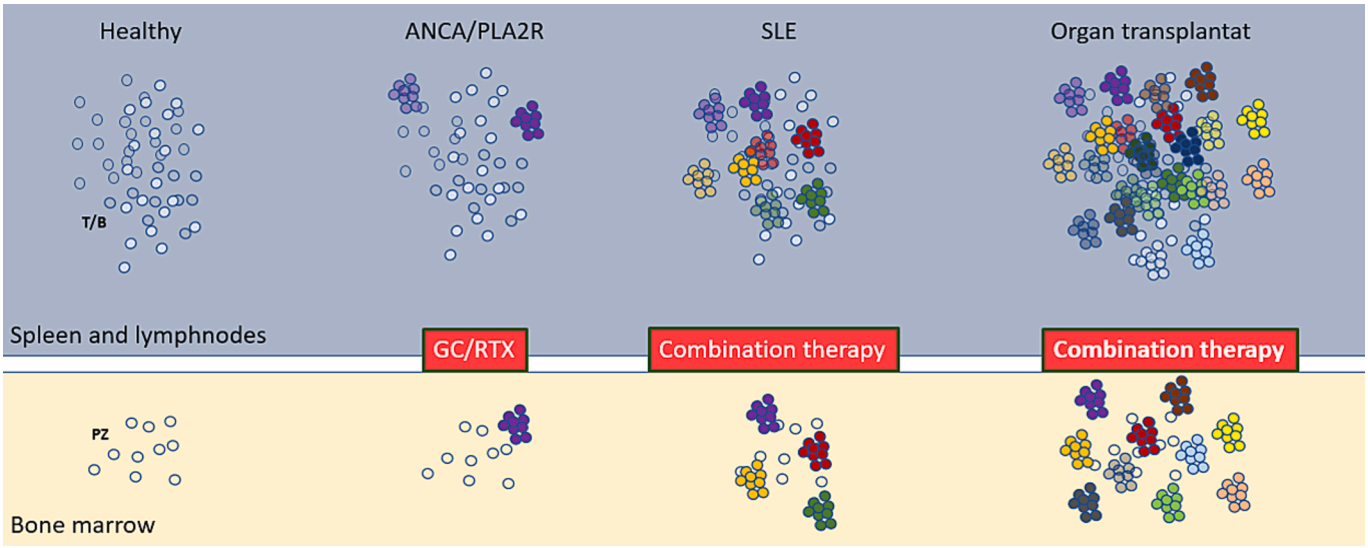

Fig. 1. The number of autoreactive T-, B-, and plasma cell clones in SLE. Immunological activity of all chronic autoimmune diseases is controlled by the size and antigen affinity of autoreactive clones of memory T cells and memory B cells (T/B) in the lymphoid organs as well as by long-lived plasma cells (PZ) in the bone marrow. In "simple" autoimmune diseases with single antigens such as, e.g., proteinase-3 in granulomatous polyangiitis or phospholipase A2 receptor in primary membranous glomerulonephritis, few immunotherapy is needed to control the few clones. In contrast, SLE involves autoimmunity against many, maybe 10–100 antigens, which goes together with a high number of T-, B-, and plasma cell clones to control, which requires combination therapy. Recipients of an organ transplant are in an even worst condition as each transplanted alloantigen will prime such a set of allo-reactive clones, which can go into the 10,000 s of clones, difficult to control even with a combination therapy. The heterogeneity of clone number, size and affinity across SLE patients explains why the same treatment regime can elicit different treatment responses from one patient to the other. What remains unclear is whether a step-up or a step-down approach is superior better in terms of long-term outcome in view of organ damage to either lack of efficacy and unnecessary drug toxicity.

3.3. The differential diagnosis of an inadequate treatment response or relapsing LN (do not call it refractory LN)

Indeed, there are several reasons why patients do not meet the usual criteria of a complete treatment response or at least a partial treatment response that are entirely unrelated to the potential of these drugs to control the immunological activity of SLE/LN. First, drug non-adherence is common with oral medications. This has been well documented for antimalarial drugs in use for SLE and likely applies the same way since when oral therapy with mycophenolate mofetil largely replaced intravenous therapy with cyclophosphamide [57,58]. In addition, concerns, and personal experience of adverse effects of glucocorticoid treatment are common and endorse drug holiday attitudes or other forms of drug non-adherence leading to insufficient control of SLE/LN. Profound patient education and shared decision making are useful means in this context [59,60], but time-consuming and sometimes face educational or cultural hurdles. Underdosing for body size or too rapid dose-taper regimes have the same result.

Second, several non-immune factors can contribute to an insufficient proteinuria response. Filtration pressure is a major determinant for the leakage of protein across an injured glomerular filtration barrier [61]. Hence, persistent causes of glomerular hyperfiltration can explain an insufficient proteinuria response, even if immunotherapy efficiently suppressed glomerular immunopathology [61]. For example, obesity (pregnancy), diabetes, and diets rich in salt or protein all impose an increased filtration pressure to kidneys [61], which may not lead to proteinuria in healthy individuals but sustain higher levels of proteinuria in patients undergoing immunotherapy for LN. The same imbalance of filtration load and filtration surface applies to patients with a low nephron number either due to developmental defects (preterm birth, genetic) or due to a previous episode of kidney injury [62]. None of these factors could be controlled by a "targeted therapy" [62]. Hence, an uncritical "step-up" treatment algorithm with targeted therapies in patients with an insufficient proteinuria response would be inadequate.

3.4. When to use targeted treatments?

Target treatments have demonstrated the potential to increase the number of patients that reach the criteria of partial and complete remission in clinical trials but it remains unclear who would have met these criteria also without these add-on medications [41,45]. Hence, who benefits from these additional medications and who not remains unknown [63]. However, this question is important because those patients not responding to standard-of-care run the risk of accumulating irreversible kidney injury during the phase of undertreatment [9]. These patients would benefit from early control of targeted therapy as promoted in the previous part of this article. In this setting, the question rather becomes an issue of financial resources. Health care systems that can afford to use targeted treatments to all patients may do so, even if many would do well also without. Health care systems with limited resources will consider to use such treatments only in those patients that show an insufficient proteinuria response in absence of the aforementioned alternative explanations drug non-adherence and co-factors promoting persistent proteinuria due to glomerular hyperfiltration. However, targeted therapies should be considered in all patients with relapsing LN, because each episode of LN involves further irreversible nephron loss and implies years of lost kidney lifespan as well as a high risk to experience ultimate kidney failure later in life [64].

3.5. How to deal with the availability of several targeted treatments?

As each LN trial tests another novel therapeutic on top of standard-of-care, it becomes difficult to decide how to use the several drug options in clinical practice. In principle, three options exist: A) Patient stratification. Mejia-Vilet et al. proposed to stratify the use of belimumab and voclosporin based on proteinuria levels in patients that do not show a decline of proteinuria by 25% from baseline within 3 months of initial therapy [65]. This approach is focused on reaching the proteinuria target of 0.8 g/g proteinuria at 12 months, which is easier to achieve with voclosporin for its potent antiproteinuric potential [45]. This approach entirely focuses on proteinuria and not on the immunological

response, which is probably more relevant for the long-term outcomes of LN. B) Dual therapy with belimumab and voclosporin would combine B cell modulation with belimumab with T cell and podocyte control with voclosporin. Such a dual targeted therapy would benefit from the synergistic mechanisms-of-action of these drugs but be the costliest treatment. C) Early dual therapy with stopping voclosporin after 6 months to control proteinuria fast followed by belimumab to secure long-term control of the autoreactive lymphocyte clones that drive SLE activity.

3.6. *Which rationale should guide the use of targeted therapies?*

Currently "treat-to-target" is discussed as a therapeutic approach for LN with proteinuria as the major determinant of treatment response [33,34,66]. However, the mechanism-of-action of drugs such as belimumab or anifrolumab is unrelated to proteinuria and rather focuses on systemic SLE activity and to prevent flares of disease [67], hence, could be rather considered more for chronic (maintenance) rather than initial (induction) therapy even if the clinical trials have been performed differently. This implies that targets are different for each drug and a general "treat-to-target" strategy may need a combination of drugs to achieve the several targets. The mechanism-of-action of each drug should guide its use in clinical practice.

4. Conclusions

Substantial advances in the management of LN have been made along the last decades, but to define the appropriate treat-to-target approach strategy can be challenging in SLE. Two drugs used on top of SoC have recently been approved for LN. In this review we discussed whether we should use the new combinatory regimens early during the disease course or in refractory patients. Main reasons to support the early use are that the RCTs carried out using these new drugs were designed to test the combinatory regimens since the beginning of LN treatment. Notably, with the combinatory regimens a higher proportion of patients achieved renal response which is well-known to reduce nephron loss and the risk of ESKD. Main reasons to save the use of the combinatory regimens after LN treatment failure are that in those RCTs some patients met the end points even without the use of combinatory regimens, which if used in those patients would lead to a waste of health care resource. However, good predictors of renal response to SoC are lacking and the different mechanisms-of-actions actually imply different treatment targets for each drug. Thus, the decision of using the new regimen early or in refractory patients should be tailored on single cases, thereby harmonizing resource availability, risk of over- or undertreatment, and preservation of renal function in higher-risk individuals.

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NC = non-collagen, Gd = galactose-deficient, GBM = glomerular basement membrane, GN = glomerulo-nephritis, PLA_2R = phospholipase A2 receptor, TSHD7A = thrombospondin type-1 domain-containing 7A, NELL = neural epidermal growth factor-like 1 protein, HTRA1 = HtrA serine peptidase 1.

CRediT authorship contribution statement

Ioannis Parodis: Conceptualization, Writing – review & editing. **Roberto Depascale:** Writing – review & editing. **Andrea Doria:** Conceptualization, Writing – review & editing, Supervision. **Hans-Joachim Anders:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

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Data availability

No data was used for the research described in the article.

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