Review

Molecular therapies for systemic lupus erythematosus: clinical trials and future prospects

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Abstract

The prognosis of patients with systemic lupus erythematosus has greatly improved since treatment regimens combining corticosteroids and immunosuppressive medications have been widely adopted in therapeutic strategies given to these patients. Immune suppression is evidently efficient but also leads to higher susceptibility to infectious and malignant diseases. Toxic effects and sometimes unexpectedly dramatic complications of current therapies have been progressively reported. Identifying novel molecular targets therefore remains an important issue in the treatment of lupus. The aim of this review article is to highlight emerging pharmacological options and new therapeutic avenues for lupus with a particular focus on non-antibody molecular strategies.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by unpredictable exacerbations and remissions with diverse clinical manifestations. The latter may range from nonspecific symptoms, such as fatigue and arthralgia, to life-threatening renal and neurological manifestations. Women of childbearing age and certain minorities are disproportionately affected. A prevalence of several hundred thousand patients with lupus has been estimated in the United States – it may in fact approach 1 million to 2 million individuals according to the Lupus Foundation of America – and almost the same figures are given in Europe.

Compared with previous decades, when the 4-year survival was estimated to be just 50% in the 1950s, patients with SLE today are less likely to die from the disease itself (the 15-year survival rate is now estimated to be around 80 to 85%). This notable improvement comes from the introduction in the 1960s and 1970s of key immunosuppressive drugs such as azathioprine, methotrexate, cyclophosphamide, and cyclosporine, and more recently by the use of mycophenolate mofetil (CellCept) that appears effective with fewer side effects. At present, antimalarials (hydroxychloroquine), corticosteroids and cytotoxic drugs are classically used as medication in SLE. It has to be recognized, however, that significant well-known adverse effects of these conventional drugs may severely counterbalance the clinical outcomes of treated patients, who can develop recurrent infections and in some cases malignant diseases. These major side effects are due to the generalized nature of the immunosuppression. There are also concerns about still unpredictable lupus flares in disease remissions and about a non-negligible number of nonresponders sometimes affected by severe forms of lupus such as catastrophic antiphospholipid syndrome.

For all these reasons, and particularly in the past 6 to 7 years, intense and collective research has led to the development of more targeted approaches that are currently under evaluation for treating patients with lupus. A number of drugs in late-stage clinical development hold promise for treating the disease. These drugs are mostly mAbs targeting B cells, such as rituxan (rituximab) or ocrelizumab (mAbs to CD20 antigen on B cells; both in phase III trial by Genentec, San Francisco, CA, USA), LymphoStat-B (belimumab; phase III trial by Human Genome Sciences, Rickville, IN, USA) that targets B-lymphocyte stimulator, and epratuzumab, a humanized antibody (Ab) that targets the CD22 receptor on B cells (phase IIb trial by UCB Pharma, Colombes, Belgium).

The present report will not concentrate on these therapeutic Abs that have been described in recent comprehensive reviews (for example [1,2]), but will rather focus on fusion

Ab = antibody; CDR = complementarity-determining region; CR = complement receptor; Crry = complement receptor 1-related protein y; CTLA-4 = cytotoxic T-lymphocyte antigen 4; DHEA = dehydroepiandrosterone; dsDNA = double-stranded DNA; IFN = interferon; IL = interleukin; mAb = monoclonal antibody; NF = nuclear factor; NZB/W = (New Zealand Black x New Zealand White)F1 lupus mice; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SNF1 = (SWRxNZB)F1 lupus mice; TLR = Toll-like receptor; TNF = tumor necrosis factor.

proteins, peptides and small molecules that represent excellent alternative tools for immune intervention in lupus.

Novel targets in the treatment of lupus patients: ongoing therapeutic trials

Molecular targeted therapies have created an encouraging trend in the treatment of lupus. In recent years, drugs targeting cell surface molecules, intracellular components, hormones or autoantigens have been clinically evaluated (Table 1 and Additional File 1).

Cell surface-expressed molecules

Based on our improving knowledge of cellular abnormalities in lupus, a variety of T-cell and B-cell surface-expressed molecules can conceptually be targeted to bypass or correct these dysfunctions. In addition to mAbs that target key cell-surface markers such as CD3, CD4, CD20, CD22, CD25 (IL-2 receptor alpha), CD52 (present on the surface of mature lymphocytes), CD40 and CD154/CD40 ligand or certain integrins, therefore, potentially efficient molecules have been developed to interfere with cell-surface components, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4)/CD152, certain members of the TNF family or members of the heat shock protein family.

Abatacept (CTLA-4 immunoglobulin; Orencia, developed by Bristol-Myers-Squibb, Princeton, NJ, USA) is a fusion protein that contains the extracellular domain of the co-stimulator receptor CTLA-4 molecule and an IgG Fc domain. Abatacept is thought to inhibit stimulation of T cells by blocking the interaction of CD80/CD86 (B7-1/B7-2) with CD28 (Figure 1). This drug, which is approved to treat rheumatoid arthritis, has been evaluated in association with prednisone in a phase IIb clinical trial for SLE, and a phase III trial for SLE is currently recruiting participants. The same company also develops belatacept (LEA29Y), which differs from abatacept by only two amino acid residues.

Atacicept, a TACI-Ig fusion protein currently evaluated in placebo-controlled phase II/III clinical trials under the sponsorshop of Zymogenetics/Merck Serono (Seattle, WA, USA and Geneva, Switzerland), targets B-lymphocyte stimulator and APRIL, two members of the TNF family, which promote B-cell survival. In an earlier phase Ib trial, patients treated with atacicept demonstrated dose-related decreases in immunoglobulin and in mature and total B-cell numbers. There was no change in the numbers of T cells, natural killer cells, or monocytes. The drug was shown to be safe and well tolerated with no serious adverse effects. There was also a positive trend in SELENA – Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores and in complement levels in treated patients [3].

Intensive research has been focused on an immunosuppressant, 15-deoxyspergualin (gusperimus; Table 1 and Additional File 1), and several active and less toxic analogues of this molecule, such as LF08-0299 (tresperimus). These molecules, the action mechanism of which is not fully elucidated, interact with the constitutive HSC70/hsp73 heat shock protein, expressed both intracellularly and at the membrane, leading among other effects to the inhibition of NF-κB nuclear translocation. 15-Deoxyspergualin was shown to suppress the progression of polyclonal B-cell activation and lupus nephropathy in lupus-prone MRL-*lpr*/*lpr* mice [4]. In a short trial, however, two out of three treated SLE patients showed nonsevere infectious episodes after 15-deoxyspergualin treatment [5].

Compounds targeting intracellular components

Targeting intracellular processes, such as signaling, apoptosis or the cell cycle, may also represent an efficient therapeutic method in SLE.

FKBP12-binding agents such as rapamycin (sirolimus, rapamune) and tacrolimus (FK506), widely used as immunosuppressive agents, may represent interesting drugs to slow down lupus disease progression. These two molecules (Table 1, Additional File 1 and Figure 1) bind to the specific cytosolic binding-protein FKBP12; but while tacrolimus complexed to FKBP12 inhibits the Ca^{2+}-dependent phosphatase calcineurin, rapamycin-FKBP12 binds to and inactivates mammalian target of rapamycin, a pivotal regulator of cell growth and proliferation for many cell types. Other effects of rapamycin include apoptosis, inhibition of T-cell activation, inhibition of cell migration, and changes in membrane trafficking. The fact that tacrolimus has been shown to reduce the incidence of skin lesions in MRL-*lpr*/*lpr* mice [6] and that it is used to control the symptoms of eczema led to the proposal that tacrolimus might represent an alternative to topical corticosteroid treatment in cutaneous lupus. It has been recently reported that tacrolimus effectively presents a significant efficacy, but randomized controlled trials are needed to evaluate its safety and cost-effectiveness [7]. Rapamycin was shown to prevent lupus in both NZB/W and MRL-*lpr*/*lpr* mice, and preliminary results in nine SLE patients revealed that rapamycin appears safe and effective in patients who have been refractory to conventional treatments [8]. A phase II study conducted by Wyeth Pharmaceuticals (Madison, WI, USA) with the aim of prospectively determining the therapeutic efficacy and action mechanisms of rapamycin in patients with SLE is currently recruiting participants.

Induction of specific apoptosis that selectively kills autoreactive or inflammatory cells should also be considered to slow down disease progression. As lupus T cells are abnormally resistant to the induction of apoptosis, targeting this population may represent an interesting alternative. Datta and colleagues have demonstrated that resistance to apoptosis of lupus T cells is related to an upregulation of cyclooxygenase 2, an enzyme involved in the formation of prostanoids [9]. Celecoxib (celebrex, celebra, controlled by Pfizer; Table 1 and Additional File 1), a cyclooxygenase-2 inhibitor, was

Table 1

Compounds of interest as new tools for the treatment of systemic lupus erythematosus

Compound	Product description	Type of study	Results/comments	Reference
Atacicept	Fusion protein (TACI-Ig) B-lymphocyte stimulator inhibition	Phase Ib, double-blind, placebo-controlled, dose-escalating trial. Patients with mild to moderate SLE were enrolled.	Dose-dependent reduction in immunoglobulin levels and B-cell numbers. Well tolerated.	[3]
15-Deoxyspergualin or gusperimus	Binds to HSC70/hsp73 heat shock protein	Case report: 3 SLE patients, safety evaluation. Treatment was performed by 9 cycles (1 cycle = 15-deoxy-spergualin administration for 14 days with a break of 7 days).	15-Deoxyspergualin was well tolerated but 2/3 patients had nonsevere infectious episodes.	[5]
FK506 or Tacrolimus	Inhibition of calcineurin	Retroprospective review: analysis of 5 studies (only one randomized controlled trial), including a total of 60 SLE patients with cutaneous lesions.	Efficacy in cutaneous lesions of SLE, but weaker efficacy in subacute cutaneous LE or in discoid LE. Studies involving only a small number of patients and no control group.	[7]
Rapamycin/sirolimus/ rapamune	mTOR inactivation	Open-label study: 9 SLE patients treated unsuccessfully with immuno-suppressive medications. Rapamycin was given orally (2 mg/day).	Reduction of BILAG score, of SLEDAI score and of prednisolone use compared with pre-rapamycin treatment.	[8]
Celecoxib or celebrex	Cyclooxygenase-2 inhibition	Retrospective review of medical records for 50 patients treated with celecoxib.	Diminution of inflammation and good safety profile.	[10]
		Prospective trial including 51 patients.	Reduction of SLEDAI score and no increase of coagulability.	[11]
Pentoxiphylline	Xanthine-derivative phosphodiesterase inhibitor	Open-label study: 11 SLE patients with refractory nephritis: class III, IV or V, proteinuria ≥3 g/24 hours.	Decrease of proteinuria (from 5.5 to 2.0, $P = 0.003$). No patients discontinued the study due to side effects.	[13]
Tamoxifen	Estrogen antagonist	Double-blind crossover trial: 11 females with stable SLE.	No improvement of disease activity and 2 patients deteriorated.	[18]
DHEA or prasterone	Androgen	Review: analysis of randomized controlled trials (7) comparing DHEA with a placebo in SLE patients (842 participants).	Little clinical effect on disease activity for patients with moderate disease.	[20]
			Modest but significant improvement in health-related quality of life.	
			Greater number of participants experiencing adverse events.	
Fulvestrant or faslodex	Estrogen receptor downregulator	Double-blind, placebo-controlled: 20 premenopausal SLE women with moderate SLEDAI received either 250 mg fulvestran intramuscularly for 12 months (10 patients) or placebo (10 patients).	Improvement of SLEDAI but not of serological markers, routine laboratory tests nor bone density. Medications for lupus reduced in the fulvestrant group.	[21]
Bromocriptine	Dopamine agonist inhibition of prolactine secretion	Open-label trial: 7 active SLE patients treated daily during 6 to 9 months.	Serum prolactine and anti-dsDNA suppressed, SLEDAI decreased (16 to 5.9).	[24]
		Double-blind, randomized, placebo-controlled: 66 SLE patients (36 bromocriptine, 30 placebo), treated daily and followed for 2 to 17 months.	Significant decreased of SLEDAI score (0.9 vs. 2.6 in control group), decreased mean number of flares/patient/month (0.08 vs. 0.18 in control group).	[25]

Continued overleaf

Table 1 (continued)

Compounds of interest as new tools for the treatment of systemic lupus erythematosus

Compound	Product description	Type of study	Results/comments	Reference
LJP394/abetimus sodium/riquent	Toleragen molecule; 4 strands of ds-oligonucleotides (20-mer) linked through a triethylene glycol-based platform	Phase III, randomized, placebo-controlled trial: 317 SLE patients with a history of renal flares and anti-dsDNA levels >15 IU/ml. Patients received 100 mg/week for up to 22 months.	Abetimus did not prolong time to renal flare, time to initiation of high-dose corticosteroid and/or cyclophosphamide treatment, or time to major SLE flare, but decreased anti-dsDNA antibody levels (P <0.0001).	[27]
Lupuzor RIHMVYSKRSGK PRGYAFIEY	21-mer peptide P140 (phosphoserine at position 140)	Phase IIa: open-label, dose-escalating trial. 20 patients with moderate SLE were enrolled. Lupuzor was given subcutaneously (200 μg or 1 mg).	Diminution of anti-dsDNA antibody levels and of SLEDAI score in the group that received 200 μg peptide.	[31]

Published trials only are presented. BILAG, British Isles Lupus Assessment Group; DHEA, dehydroepiandrosterone; ds, double-stranded; mTOR, mammalian target of rapamycin; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

shown to induce apoptosis of lupus T cells *ex vivo*, leading in co-cultures to the inhibition of autoAb production [9]. Results from two clinical trials including SLE patients revealed that the use of celecoxib, which presents a good safety profile, was beneficial with, notably, a decrease of generalized inflammation and a decreased SLEDAI score [10,11].

Cyclic nucleotide phosphodiesterase isoenzymes (11 families), dedicated to cyclic AMP/GMP hydrolysis, play an important role in physiological responses. The PDE4 family was described as one of the major families controlling inflammation, and over the past years the development of PDE4 inhibitors as anti-inflammatory drugs has been a major focus of pharmaceutical research. The administration of pentoxiphylline (Table 1 and Additional File 1), a xanthine derivative and well-known phosphodiesterase inhibitor, into MRL-*lpr*/*lpr* mice resulted in a diminution of clinical parameters of the disease [12]. In an open-label study including 11 lupus patients with renal manifestations, pentoxiphylline was demonstrated to reduce proteinuria [13]. Further investigations should thus be undertaken to validate this interesting observation as all patients were given immunosuppressants concomitantly.

Agents that modulate the hormonal pathway

Both sex steroid estrogen and pituitary hormones such as prolactin are known to modulate autoimmunity and are thus supposed to play a role in SLE. The involvement of hormones in disease pathogenesis is supported by several observations: the prevalence of SLE is far higher in females than in males; the onset of lupus often occurs in young, premenopausal women; and males with SLE have low levels of testosterone. The reduced secretion of anti-DNA Abs following testosterone treatment highlights the critical role of estrogen in the disease.

Modulation of sex steroid hormones

Treatment of NZB/W female mice with the estrogen antagonist tamoxifen (Table 1 and Additional File 1) significantly reduces anti-DNA Ab production, ameliorates glomerulonephritis and prolongs survival [14,15]. In MRL-*lpr*/*lpr* female mice, tamoxifen alleviates disease activity, and treatment with the selective estrogen receptor modulator LY139478 (Table 1 and Additional File 1) improves survival and retards the progression of glomerulonephritis [16,17]. An open-label study of 11 patients with SLE, however, did not demonstrate any benefits of tamoxifen in ameliorating the clinical and serological activity of SLE [18].

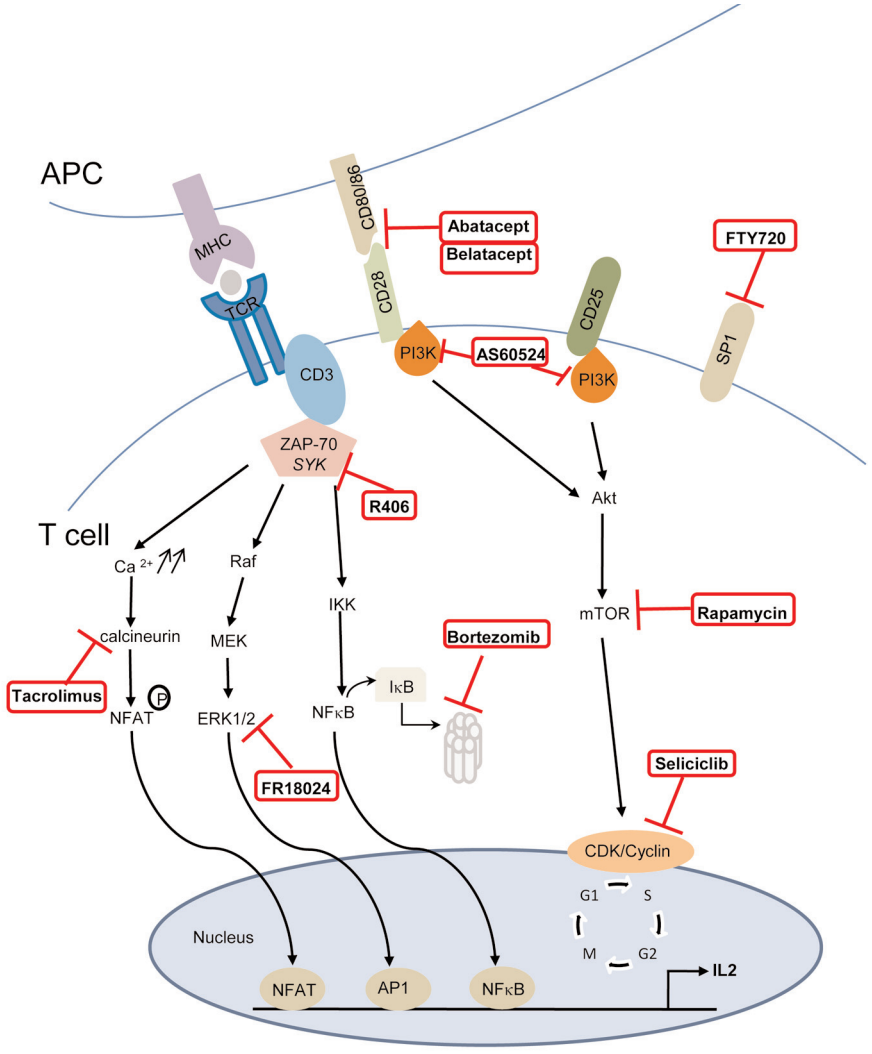
Improvement of the lupus disease in animal models with androgen administration led investigators to also consider dehydroepiandrosterone (Table 1 and Additional File 1) for therapeutic use in lupus patients. Dehydroepiandrosterone (DHEA) is a naturally occurring steroid and possesses both endocrine and immunomodulatory effects. Interestingly, serum levels of DHEA are decreased in SLE patients [19]. Several clinical studies have thus investigated the effect of DHEA (G-701, prestara, prasterone) administration in lupus patients. A comparison of these studies revealed that whereas DHEA supplementation improved quality of life and glucocorticoid requirements, the impact on disease activity was inconsistent [20].

A double-blind placebo-controlled clinical trial recently reported encouraging results in SLE women treated with an estrogen-selective receptor downregulator named fulvestrant (faslodex, developed by AstraZeneca Pharmaceuticals, London, UK; Table 1 and Additional File 1). In patients who received 250 mg fulvestrant intramuscularly for 12 months, the SLEDAI score improved significantly and conventional medications could be reduced [21].

Inhibition of prolactin

An increased frequency of hyperprolactinemia is observed in patients with SLE, and elevated prolactin levels have been correlated with clinical disease [22]. Prolactin administration has been demonstrated to accelerate disease progression in

Figure 1



Intracellular components targeted by non-antibody-directed therapeutics in lupus. Activation of the T-cell receptor (TCR) promotes a number of signaling pathways, which may be targeted to treat systemic lupus erythematosus. Drugs that have been evaluated in lupus are indicated in red boxes. Akt, protein kinase B; AP1, activator protein-1; APC, antigen-presenting cell; CDK, cyclin-dependent kinase; ERK, extracellular signal-regulated kinase; IKK, IκB kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; NFκB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; SP1, sphingosine-1-phosphatase receptor; SYK, spleen tyrosine kinase; ZAP-70, z-chain associated protein kinase.

murine models of lupus (reviewed in [23]). Taken together, these data showed that downregulation of the prolactin production may represent an interesting way to treat SLE.

As prolactin secretion is inhibited by dopamine released from the hypothalamus, the efficacy of bromocriptine (Table 1 and Additional File 1), which is a dopamine agonist, was evaluated in lupus. In an open-label trial including seven SLE patients, it was shown that bromocriptine (3.75 to 7.5 mg/day for 6 months) suppressed prolactin levels in all subjects and improved clinical measurements in six of the seven treated patients [24]. A double-blind, placebo-controlled study of low-dose bromocriptine therapy (2.5 mg/day) showed a significant decrease in prolactin levels associated with a significant decrease in disease activity [25]. A pilot clinical trial was recently conducted to explore the potential role of oral bromocriptine during pregnancy [26]. Results showed that bromocriptine may play a role in protecting pregnant lupus patients from maternal and fetal complications.

Autoantigens

Among the outcome measures (endpoints) to be considered in SLE trials are biomarker manifestations (for example, anti-dsDNA Abs). During the past decade, a number of investi-

gators have thus explored targeted strategies involving autoantigens in order to subvert or block key steps of the disease. Promising data have been raised in murine models of lupus, and a few therapeutic trials are currently in progress.

Two peptides and one peptide construct have reached advanced clinical trials in lupus patients. The efficacy of the first peptide, hCDR1 (edratide, TV-4710), although extremely promising in lupus mice, was found to be safe and well tolerated but did not meet its primary endpoint in a randomized, double-blind, placebo-controlled phase II clinical trial conducted by Teva (Petach Tikva, Israel) in 340 SLE patients who received the peptide weekly by a subcutaneous route (PRELUDE trial).

The results of a second candidate, abetimus sodium (LJP394, riquent) – evaluated in a randomized, placebo-controlled, multicenter phase III trial – have been recently published [27] (Table 1 and Additional File 1). Abetimus is a synthetic water-soluble molecule consisting of four double-stranded oligodeoxyribonucleotides each attached to a nonimmunogenic triethylene glycol backbone, a proprietary carrier platform [28]. Originated by La Jolla Pharmaceuticals (San Diego, CA, USA), abetimus is an immunomodulating agent that induces tolerance in B cells directed against dsDNA by cross-linking surface Abs potentially responsible for lupus nephritis. The recent reported data showed that abetimus administrated at 100 mg/week for up to 22 months to patients with lupus nephritis significantly reduced anti-dsDNA Ab levels but did not significantly prolong the time to renal flare when compared with placebo. Although multiple positive trends in renal endpoints were observed in the abetimus treatment group [27], it has been recently decided to halt further clinical trials of this drug in lupus.

A third peptide-based strategy involving an autoantigen segment, peptide P140 (IPP-201101, lupuzor), holds promise (Table 1 and Additional File 1). This phosphorylated peptide is recognized by T cells from MRL-*lpr/lpr* mice and patients with SLE [29,30]. Intravenous administration of P140 into MRL-*lpr/lpr* mice was found to significantly improve their clinical and biological manifestations and prolonged their survival, while the nonphosphorylated analogue did not. The P140 peptide was included in phase I and phase II clinical trials conducted by ImmuPharma (Mulhouse, France). Peptide P140 was found to be safe and well tolerated by subjects, and significantly improved the SLEDAI score and biological status of lupus patients who received three subcutaneous doses of 200 µg peptide [31]. P140 peptide is currently being evaluated in a phase IIb, double-blind, placebo-controlled, dose-ranging study in Europe and Latin America to confirm the beneficial effects observed in the phase IIa trial.

Experimental agents for lupus therapy

Beside agents that are presently evaluated in clinical trials in patients with lupus, there are also a number of experimental compounds used with success in murine studies that deserve particular attention. They are described below because hopefully some of them represent interesting candidates for future clinical trials.

Compounds targeting intracellular components

Spleen tyrosine kinase, a cytoplasmic tyrosine kinase, is a key mediator of immunoreceptor signaling in a variety of cells, including B cells, mast cells, macrophages platelets, and naïve mature T cells. The spleen tyrosine kinase-specific inhibitor R406 (converted from the prodrug R788 developed by Rigel Pharmaceuticals Inc., San Francisco, CA, USA), given orally, reduced the renal pathology and prolonged survival of prediseased NZB/W mice, and, more importantly, of mice with established lupus nephritis [32]. Interestingly, signaling in lupus T cells is not effected by ZAP-70 but replaced by spleen tyrosine kinase, leading to an increased calcium response upon T-cell receptor stimulation [33].

Although no clinical data from SLE lupus are yet available, results from a recent phase II clinical trial including 189 patients with rheumatoid arthritis are encouraging [34]. The use of small molecules inhibiting intracellular mitogen-activated protein kinase and phosphoinoside 3-kinase (enzymes that generate phosphatidylinositol diphosphate and triphosphate after receptor stimulation) signaling pathways has also been envisaged. Although the extracellular signal-regulated kinase (a serine/threonine protein kinase of the mitogen-activated protein kinase family) inhibitor FR180204 was recently described as a new therapeutic approach in rheumatoid arthritis [35], the use of such molecules in lupus could be hampered by the fact that the mitogen-activated protein kinase/extracellular signal-regulated kinase kinase pathway is reduced in lupus T cells [36]. In contrast, several studies have demonstrated that phosphoinoside 3-kinase gamma plays a crucial role in SLE, and encouraging results have been obtained using MRL-*lpr/lpr* mice treated with selective phosphoinoside 3-kinase gamma inhibitors, such as AS605240 (a specific p110γ inhibitor) [37]. Promising molecules targeting the phosphoinoside 3-kinase pathway that have entered clinical trials for cancer therapy, inflammation and coronary heart disease are described in a recent review [38].

Molecules able to interfere with cell cycle should also be considered as potential candidates in the development of new lupus therapies. Cell cycle progression is controlled by the activation of a heterodimer, formed by cyclins (regulatory subunits) associated with cyclin-dependent kinases (catalytic subunits; Figure 1). The effect of seliciclib (CYC202; Table 1 and Additional File 1), a cyclin-dependent kinase inhibitor that is a trial drug currently tested in patients with solid tumors and B-cell malignancies, was recently evaluated in NZB/W lupus mice [39]. When administered in the early stages of the disease, seliciclib was shown to delay the development of proteinuria, to reduce the production of anti-dsDNA Abs, and

to prolong survival. A similar observation was made with the use of a cell cycle peptide inhibitor, the $p21^{Waf/Cip1}$ mimic [40]. As the expression of the cyclin-dependent kinase inhibitor $p21^{Waf/Cip1}$ is decreased in lymphocytes of lupus patients [41], the use of such inhibitors could represent an attractive route for treatment.

Other agents for which efficacy has been already established in murine models of lupus may offer interesting therapeutic avenues in the future. The ubiquitin–proteasome pathway is involved in intracellular protein turnover and its function is crucial to cellular homeostasis. Bortezomib (a proteasome inhibitor marketed as Velcade by Millennium Pharmaceuticals, Cambridge, MA, USA; Table 1 and Additional File 1) has thus been successfully used in multiple myeloma. By blocking IκB degradation, bortezomib induces the inhibition of NF-κB and increases apoptosis of leukemia cells. These results led investigators to evaluate the efficacy of bortezomib for the depletion of plasma cells in lupus. Bortezomib treatment of NZB/W and MRL-*lpr/lpr* lupus mice efficiently depleted plasma cells, reduced autoAbs production, ameliorated glomerulonephritis and prolonged survival [42]. It was recently shown that inhibiting proteasome does induce the apoptosis of activated $CD4^+$ T cells, indicating that targeting proteasome activity in lupus may represent an interesting molecular strategy for targeting both autoreactive B cells and T cells.

Histone acetylation is an important regulator of gene expression, and therefore interfering with histone deacetylation could represent an interesting strategy to modulate altered gene expression in lupus. Histone deacetylase inhibitors have been used to reduce the disease in murine models of lupus. In MRL-*lpr/lpr* mice, tricostatin A (Table 1 and Additional File 1) was found to decrease inflammatory cytokine production by splenocytes and reduce renal disease [43]; suberoylanilide hydroxamic acid was also shown to modulate lupus progression [44]. These experimental data suggest that histone deacetylase inhibitors might have therapeutic interest to treat SLE.

Compounds inhibiting soluble molecules

In lupus, the loss of self-tolerance leads to the persistence and activation of autoreactive B cells and T cells with the consecutive abnormal secretion of cytokines and production of autoAbs. The formation of immune complexes and the activation of the complement pathway also play a major role in disease pathogenicity. These soluble proteins are thus interesting target candidates for the development of novel lupus therapies.

The activation of the complement pathway in lupus amplifies both immune and inflammatory responses and is involved in the renal pathology. Apart from the use of anti-C5 monoclonal Abs, the recent development of a molecule able to interfere with both alternative and classical complement pathways and that protects MRL-*lpr/lpr* mice from the disease is encouraging [45]. This therapeutic agent, named CR2-Crry, corresponds to a fusion protein that links the C3-binding region of complement receptor 2 (CR2) to the complement receptor 1-related protein y (Crry). Crry is similar to human complement receptor 1 and inhibits C3 convertases of all pathways. Complement inhibition in MRL-*lpr/lpr* mice with Crry as a recombinant protein (Crry-Ig) protected animals from renal disease but had no effect on survival [46], whereas CR2-Crry treatment reduced glomerulonephritis, renal vasculitis, skin lesions and autoAb production associated with a significant survival benefit. Importantly, and contrary to observations with Crry-Ig, CR2-Crry did not increase the levels of circulating immune complexes, offering another advantage to its development for controlling the human disease.

Several cytokines have been identified as major targets in lupus, leading to the development of numerous mAbs, some of them currently used in therapy or under clinical evaluation. Another approach was recently developed, based on active immunotherapy, which consists of inducing Abs able to neutralize the interaction of the self-cytokine to its receptor. In a mouse model for rheumatoid arthritis (transgenic mice expressing human TNFα), it was demonstrated that vaccination with a biologically inactive but immunogenic human TNFα derivative (keyhole limpet hemocyanin–human TNFα heterocomplex), led to the production of high titers of Abs that neutralize human TNFα bioactivity. Moreover, immunized transgenic mice were protected from spontaneous arthritis [47]. As cytokine network dysregulation is highly complex in lupus, further investigations are needed to evaluate whether this strategy may be advantageous in SLE in the future.

FTY720 (fingolimod), a high-affinity agonist of sphingosine-1-phosphate type 1 receptor that induces the internalization of the receptor, thus depriving cells from normal binding of soluble sphingosine-1-phosphate type 1, is effective in several murine models of lupus. The agonist was found to suppress the development of autoimmunity and to prolong the lifespan of female MRL-*lpr/lpr* mice [48]. FTY720 acts primarily by sequestering lymphocytes within peripheral lymphoid organs, rendering them incapable of migrating to the sites of inflammation. Phase I, phase II and phase III clinical trials have been conducted mostly in patients with multiple sclerosis (Novartis, Basel, Switzerland) (reviewed in [49]). Results are not yet available for patients with SLE.

Autoantigens

As described above, peptides encompassing autoantigen sequences represent interesting tools to specifically target autoreactive cells. Beside the peptides currently evaluated for their efficacy in lupus, other peptides hold promise as they gave interesting results in murine models of lupus.

Peptides corresponding to complementary-determining regions (CDRs) in the heavy chain variable domain of autoAbs to

dsDNA have thus been used with remarkable efficacy in NZB/W mice. These are, for example, the so-called 15-mer pCONS peptide, a consensus of sequences derived from the immunoglobulin heavy chain variable region (CDR1 and second framework FR2) of several different NZB/W Abs to DNA [50], or peptides derived from the sequence of the CDR1 and CDR3 (pCDR1, pCDR3) of a murine anti-DNA mAb that bears the so-called 16/6 idiotype [51]. Tolerization of NZB/W mice to monthly intravenous injections of 1 mg pCons significantly delayed the appearance of multiple Abs and nephritis, and dramatically prolonged survival of treated mice. Tolerization with pCons, which contains MHC class I and II T-cell determinants, was shown recently to activate different subsets of inhibitory/cytotoxic $CD8^+$ T cells that regulate both $CD4^+CD25^-$ effector T cells and B cells [52]. The tolerogenic 19-mer human CDR1 (hCDR1) peptide designed by Mozes and colleagues was found to interfere with murine lupus disease via the induction of $CD4^+CD25^+$ regulatory T cells, and suppression involves $CD8^+CD28^-$ regulatory T cells [53]. As mentioned above, however, this peptide did not give expected results when evaluated in lupus patients.

Regarding peptides from nuclear autoantigens, Datta and colleagues showed that repeated intravenous or intraperitoneal administration into (SWRxNZB)F1 (SNF1) lupus mice with established glomerulonephritis of a single peptide of histone H4 (sequence 16 to 39), which behaves as a promiscuous T-cell epitope, prolonged survival of treated animals and halted progression of renal disease [54]. The protective properties of another peptide of histone H4 (sequence 71 to 93), accompanied by an increased level of IL-10 and suppression of IFNγ secreted by lymph node cells, were described in SNF1 mice administrated by the intranasal route [55]. Following intranasal (but not intradermal) administration of H4 peptide 71 to 93, the number of $CD4^+CD25^+$ regulatory T cells, which is low in NZB/W and SNF1 mice as compared with normal mice, was restored in both strains [56]. Very low-dose therapy (1 μg given subcutaneously every 2 weeks) of SNF1 mice with H4 peptide 71 to 94 was also found to induce $CD8^+$ and $CD4^+CD25^+$ regulatory T cells, to decrease IFNγ levels secreted by pathogenic T cells, and to decrease the Ab levels by 90 to 100% [57]. The histone H3 peptide 111 to 130 encompassing a T-cell epitope in NZB/W mice was used with success when administrated intradermally in Freund's adjuvant into these mice [58]. Treatment of MRL-*lpr/lpr* mice with a 21-mer peptide of the laminin α-chain targeted by lupus Abs also prevented Ab deposition in the kidneys, ameliorated renal disease, decreased the weight gain caused by accumulating ascitic fluid and markedly improved the longevity of treated mice [59].

Prospectives

Recent publications describing the successful use of new therapeutic agents in murine models support their further evaluation as therapies for SLE. In lupus, therefore, the therapeutic potential of targeting Toll-like receptors (TLRs) is supported by recent studies involving TLR7 and TLR9. Nonstimulatory DNA sequences, able to inhibit TLR7 and TLR9 activation and referred to as immunoregulatory DNA sequences, have been identified. Interestingly, the administration of one of these immunoregulatory DNA sequences to NZB/W mice significantly reduced autoAbs production and proteinuria, and increased survival [60].

In MRL-*lpr/lpr* mice, the administration of a synthetic G-rich DNA (named ODN 2114) known to block CpG-DNA effects led to less autoimmune tissue injury in the lungs and kidneys, accompanied by decreased serum levels of anti-dsDNA IgG_{2a} Abs and of IFN-α [61]. The fact that chronic overproduction of IFNα may represent another marker for disease activity in lupus [62] underlines the interest for the evaluation of such immunoregulatory DNA sequences in SLE patients.

Statins are also considered with great interest since it was demonstrated that these cholesterol-lowering drugs have immunomodulatory properties. Additional studies are required to investigate the potential use of statins in lupus, however, as contradictory results were obtained in NZB/W mice that were given atorvastatin, either orally or intraperitoneally.

Conclusions

The current literature search shows a number of promising molecules that are impressively efficient in murine models of lupus. These widely used mouse models are of first importance to identify decisive novel targets, to examine newly developed therapeutic tools and to determine/clarify the mode of action of these new molecules *in vivo*. Clearly, however, very few of these molecules reach the standard required for evaluating them in clinical trials involving patients with SLE (their solubility and bioavailability, in certain cases, can represent an important limitation). Moreover, because SLE is a syndrome with multiple manifestations, both clinical and biological, management and endpoint determinations of clinical trials for SLE are complex. In particular, a central question concerns the validity of biomarkers (and surrogate markers) and activity indices, which are pertinent for evaluating the performance of lupus trials [63,64].

Important progress has been made recently with the publication of guidelines aimed at facilitating and better controlling clinical trials for SLE [65]. Managing patients with SLE is challenging and new treatments are eagerly awaited. Establishing a valuable and solid data monitoring of patients is as crucial as designing and developing safe and efficient therapeutic molecules or biologicals.

Competing interests

Both authors hold patents on P140 peptide (holder: Centre National de la Recherche Scientifique [CNRS], licence to ImmuPharma). FM has received post-doctoral funding from CNRS and ImmuPharma. SM has received fees from

ImmuPharma to support part of the research activity of her laboratory, the CNRS research unit.

Additional file

The following Additional file for this article is available online:

Additional file 1 is a Word document comprising of an expanded version of Table 1, incorporating graphic representations of each compound. See http://arthritis-research.com/content/supplementary/ar2711-s1.doc.

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