
Review Article

New Targets in Systemic Lupus (Part 2/2)∗

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ABSTRACT

Glucocorticoids, aspirin, conventional antimalarials and immunosuppressants are the mainstay of treatment of Systemic Lupus Erythematosus (SLE). Until recently, the first three were the only agents approved for treatment. A better understanding of the pathophysiology of the immune system has identified new therapeutic targets. In fact, belimumab, a human monoclonal antibody to BLyS inhibitor has become, in recent months, the first drug approved for the treatment of SLE since 1957, underscoring difficulties of all kinds, including economic and organizational ones inherent to clinical trials on this disease. Many other molecules are in various stages of development and soon will have concrete results. In this review, we examined the mechanism of action and most relevant clinical data for these molecules.

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Nuevas dianas terapéuticas en el lupus sistémico (parte 2/2)

RESUMEN

Glucocorticoides, aspirina, antimaláricos e inmunosupresores convencionales constituyen la base del tratamiento del lupus eritematoso sistémico (LES). Hasta recientemente, los 3 primeros eran los únicos agentes aprobados para su tratamiento. El mejor conocimiento de la fisiopatología del sistema inmunitario ha permitido identificar nuevas dianas terapéuticas. De hecho, belimumab, un anticuerpo monoclonal humano inhibidor de BLyS, se ha convertido hace pocos meses en el primer fármaco aprobado para el tratamiento del LES desde 1957, lo que subraya las dificultades de todo tipo, incluyendo las económicas y organizativas, inherentes a los ensayos clínicos sobre esta enfermedad. Otras muchas moléculas se encuentran en distintas fases de desarrollo y en poco tiempo dispondremos de resultados concretos. En esta revisión repasamos el mecanismo de acción y los datos clínicos más relevantes de estas moléculas.

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Inhibition Survival Factor B

The second way to deplete B cells is the inhibition of differentiation and survival of these cells, APRIL and BLyS, also known as BAFF (B cell activating factor), 2 cytokines of the TNF superfamily. BLyS may bind 3 different receptors on the surface of B lymphocytes (BL), the receptor for BLyS (BLySr or BR3), TACI (transmembrane activator and calcium modulator ligand interactor) and BCMA (B cell maturation antigen); APRIL may bind only 2: TACI and BCMA. Both BLyS and APRIL promote B cell differentiation and survival and their inhibition leads to B cell depletion, fundamentally apoptosis, and a reduction in antibody production.1–3 specific inhibitors of BLyS have been developed (belimumab, AMG-623 and briobacept) and a fusion protein, atacicept, which inhibits both BLyS and APRIL.1

Belimumab (Benlysta®, LymphoStat-B®), is a completely human monoclonal antibody that inhibits the biological activity of BLyS (BAFF). Although its mechanism of action is not completely understood, it seems to inhibit the stimulation of BL and reestablish the potential for autoreactive BL to suffer apoptosis. Therefore, a reduction in circulating BL is achieved, though less profound and prolonged than that produced by anti-CD20.

Clinical development of belimumab has passed through 2 stages: a phase II initial stage carried out in 449 patients with non renal and non neurological SLE, including 28% with negative ANA, which did not find differences in SLEDAI variations or the number of flares when compared to placebo2; however, a second,
its approval by the FDA in March 2011 as a treatment for SLE in
leukemia and a significant reduction on autoantibodies. This led to
improvements in immunologic parameters, normalization of hypergammaglobu-
linemia and a reduction in autoantibody levels, without an increase in adverse
events. These new results sustained the development of two ambitious
phase III trials, one with a 52-week evaluation of 865 patients (BLISS-52) and another lasting 76 weeks including 826 patients (BLISS-76), finding improvement, although not overtly superior, compared to placebo (57% vs 43%), but with an important change (BLISS-76), finding improvement, although not overtly superior,
in combination with standard therapy, thus becoming the first drug
approved for the treatment of this disease since 1957.3

Briabacept (BR3-Fc). It is a recombinant glucoprotein formed by
2 molecules from the BlyS receptor (BR3) joined to the Fc domain of
human IgG1. BR3-Fc binds BlyS (BAFF) but not APRIL. Experimental
studies in monkeys showed an effect by BR3-Fc in B cell subpopu-
lations: CD21IbH, homologous to human marginal zone B cells and naïve B cells, which suffered more depletion than memory B cells.
A yet unpublished trial in human SLE has been performed.

Atacicept (TACI-Ig). TACI-Ig is a recombinant fusion protein that
stimulates the soluble TACI receptor and blocks activities of
both BlyS and APRIL. Preclinical modeling showed that atacicept
produces a profound depletion of plasma cells, something that led to
the development of phase I trials with results in line to what
would be expected by their mechanism of action, in addition to hav-
ing a comfortable subcutaneous weekly administration.4 A phase II
trial in combination with mycophenolate mofetil for the
treatment of LN was suspended due to an increased number of
infections. However, a phase III trial for non-renal SLE is underway
(APRIL-SLE).

AMG 623 (blislimimod). Is a peptibody (a hybrid of a small pep-
tide and an antibody) that acts as a decoy of BlyS, binding it and
impeding the interaction with its receptor on B cells, with a phase II trial underway.

Inhibitors of T Cell Costimulation

Production of autoantibodies by B cells requires activation and
collaboration of T lymphocytes (TL) and this activation needs at
least two signals from antigen presenting cells (APC). The so-called
“first signal” takes place through the recognition of antigen on the
part of the T cell receptor (TCR), when the former is presented
to it in the context of the major histocompatibility complex of
the APC. After this signal, the TL expresses a CD28 molecule on
its surface, which interacts with its ligands B7-1 (CD80) and B7-
2 (CD86), present on the surface of APCs, constituting a “second
signal” CD28/B7, which completes T cell activation. Following this
second signal, the TL proliferates, differentiates, produces cytokines
and expresses new costimulation molecules on its surface which
interact with their corresponding ligands on the APC, and give
rise to a succession of inhibitory and stimulatory signals that have
the objective of controlling the effector actions of TL. However,
CD28/B7 interaction not only sends costimulatory signals to the TL,
but also to the APC, which receives feedback and, as would occur
on the TL, responds with the expression of successive inducible
ligands on its surface and the synthesis of cytokines, IL-6, among
others, a cytokine known for its direct or indirect “inflamma-
tory” profile acting through the differentiation of naïve Th17 T
cells. Therefore, inhibition of costimulatory molecules has multiple
consequences on immunity and is the motive that these molecules
are under intense research as therapeutic targets. Among the
receptor/ligand sets, some have agonist actions, such as the above
mentioned CD28/B7 or those formed by CD40/CD40L, ICOS/ICOS-
L, OX40/OX40L and 4-1BB/4-1BBL, and some have an inhibitory
effects, such as CTLA-4 (cytotoxic T lymphocyte antigen 4), also
known as CD152, with B7-1 and B7-2, which inhibit or attenuate
the autoimmune process.5

CD28-B7-1/B7-2 Blockage

After the first signal, the expression of CD28 is induced on TL,
which will interact on its ligands B7-1 (CD80) and B7-2 (CD86),
present on the APC; the resulting intracellular signaling cascade has
an agonist effect that leads to the activation of transcription factors
that will culminate in the expression of IL-2 and TL proliferation.

Anti-CD28 (TG11412). The initial strategy to block costimulation
via CD28 consisted in the administration of a monoclonal anti-CD28
antibody, with the intention of inhibiting its binding to its natural B/family ligands; however, anti-CD28/CD28 binding had a potent
agonist effect on TL, with massive production of cytokines which
led to a severe systemic reaction and multiorgan failure, a phe-
nomenon called a “cytokine storm” which led to research into this
drug being suspended.6

CTLA4-IgG (abatacept, Orencia®). Better known for its use in RA,
it is a fusion protein that combined an extracellular domain of CTLA-
4 bound to the Fc fragment of human IgG1. Abatacept binds B7-
1(CD80) and B7-2(CD86), with greater affinity than for CD28 and
acts as a competitive inhibitor of the CD28/B7 interaction, impeding
T cell costimulation through CD28 and, therefore, signaling that
would lead to T cell proliferation and the production of cytokines;
the consequence is that the T cell becomes anergic or apoptotic. The
only phase II study in SLE with abatacept did not attain the proposed objectives which were a reduction in the number of flares, time
to the appearance of a flare and the number of flares while treated
with steroids; in addition, adverse events were more frequent in the
active arm than in the placebo arm.7 However, a post hoc analysis
in which the definition of flare was modified from a new BLILAG A or
B to a only a new BLILAG A, managed to reduce the number of flares
significantly compared to the placebo group. This led researchers
to propose a new trial, in relation to LN, which is underway.

Belatacept (LEA29Y). A molecule with the same principle as abat-
accept, of which it can be considered a modification; it offers the
advantage of having much higher affinity for its ligands B7-1 and
B7-2. It has been tried out in RA but not in SLE.

CD40/CD40L Blockage

The interaction of CD40, a molecule expressed on BL, den-
dritic cells and other APCs, with its ligand CD40L (CD154, gp39),
expressed on activated T CD4 and T CD8 and NK cells, among
others, is essential in generating a B cell dependent T cell response.
This costimulating pair transmits signals both for T cells and APC
that express B7 and, therefore, leads to T cell proliferation. As a
consequence, the interruption of CD40/CD40L costimulation is a
therapeutic strategy that has been attempted with 2 anti-CD40L
monoclonals: ruplizumab, talorizumab and ABI 793.

Ruplizumab (BG9588). It was in a small trial with 28 LN type
IV patients, interrupted due to a high incidence of thromboem-
bolic events and myocardial infarctions, pulmonary embolus and
strokes, including one death. The analysis of the results at the
moment of interruption showed a reduction in hematuria and the
anti-DNA titer, as well as an increase in C3.8

Toralizumab (IDC-131, E6040, anti-gp39). A clinical trial of
toralizumab vs placebo in mild to moderate SLE found no throm-
boembolic events but neither did it find clinical efficacy.9 The
development of the drug was abandoned after a patient in a Crohn’s disease trial suffered a thromboembolic event.

ABI 793. Once again, cardiovascular events were responsible for stopping the development of this completely humanized monoclonal antibody, suggesting that thromboembolic complications are a class effect of anti-CD40L antibodies.

OX40/OX40L and ICOS/ICOS-L Blockage

OX40 is expressed on T cells while OX40L does so on dendritic cells, B cells and macrophages. OX40/OX40L stimulates proinflammatory cytokine secretion on the part of APC. A phase II trial is currently underway with an anti-OX40L antibody in patients with asthma, but no trials exist for SLE.

The interaction of ICOS, a molecule expressed on T cells, with ICOS-L (CD275), expressed mainly on B cells, leads to the synthesis of IL-4 and IL-10. ICOS/ICOS-L blockage is currently being tested with an anti-ICOS-L antibody (AMG 557) in a phase I trial with lupus patients.

Adhesion Molecules

Binding between the TCR and the APC is highly specific, but with low affinity and the stabilization of this binding is carried out through cellular adhesion molecules (CAM), which have also been considered as therapeutic targets for autoimmune diseases, although none have been tested in SLE.

Efalizumab (Raptiva®). Efalizumab is an anti-LFA1 monoclonal antibody that inhibits ICAM1/LFA1 interaction. Because LFA1 mediates binding of leukocytes to the endothelium, and their subsequent margination into tissues, treatment with anti-LFA1 should lead to a reduction in inflammatory cell infiltrates in tissues. Efalizumab was even approved for the treatment of plaque psoriasis, but the EMEA suspended its sale in Europe because it produced progressive multifocal leukoencephalopathy.

Alefacept (Amevive®). Is a LFA3-IgG fusion molecule that is used for the treatment of psoriasis. Alefacept interferes with T cell activation through preventing the binding between CD2 on TL, and LFA-3 (CD58), on APC, something that allows for the stability necessary for both cells to interact.

Natalizumab (anti-α4-integrina, Tysabri®). Inhibits the interaction between integrins and VCAM1 (vascular cell adhesion molecule 1). It has been approved for the treatment of MS and Crohn’s disease, although some restrictions are in place due to its association with focal progressive leukoencephalopathy.

The appearance of focal progressive leukoencephalopathy cases are not exclusive to this group but do appear relatively frequent in relation to it, elevating the suspicion that these drugs reduce immunologic surveillance of the JC virus and facilitate the expansion of a preexisting latent infection.

T Lymphocytes

TL have a central role in the development of tolerance and autoimmunity. Diverse anomalies in intracellular signal transduction in T cells have been described in SLE, among them, a change in the complex formed by the TCR and its associated protein CD3 (TCR complex), which produces an increase in the initial events in signaling, leading to an exaggerated transduction and, in consequence an abnormal expression of cytokines. This justifies that the elevated capacity T cells have to stimulate BL to produce autoantibodies and explains the survival of autoreactive TL through a reduced rate of cell death, all of this resulting in the loss of tolerance that characterizes SLE. This and other, several reasons have made TL an interesting target in autoimmune diseases. However, we are faced with a difficult cell to approach, both for the subpopulations it has as for the interactions among them and other elements of the immune system. The diverse strategies used vs TL allow reaching a specific state of tolerance through depletion therapy, costimulatory molecule blocking, already commented upon, or acting over regulating TL.

T Cell Depletion

Several biologic agents have been developed to obtain TL depletion, all of them studied in RA, where they did not achieve satisfactory results, but although hypothetically useful in SLE, have not been tested in this disease.

Anti-CD52 (CAMPATH-1, alemtuzumab). CD52 is expressed on the surface of B, T CD4, T CD8 and NK cells, dendritic cells, thymocytes, monocytes-macrophages and eosinophils. The monoclonal anti-CD52 antibody is particularly employed in chronic lymphocytic leukemia but has shown some usefulness in autoimmune diseases such as MS. In spite of its abundant expression in a wide array of cells, alemtuzumab leads to an especially prolonged and intense depletion of CD4+ TL, with severe adverse events and limiting its usefulness.

Anti-CD3. CD3 is expressed in all TL and along with the TCR forms the TCR complex. The first biologic, approved 25 years ago for avoiding organ rejection, was OKT3 (murinomab), a mouse monoclonal antibody which saw limited use due to the frequent development of antinouse antibodies and because it stimulated TCR and activated T cells producing a massive liberation of cytokines. Visilizumab represents a new generation of anti-CD3, which on the one hand is a humanized antibody and on the other hand has suffered manipulation of its Fc to reduce the interaction with its receptor and, therefore, T cell activation and the massive production of cytokines. Its mechanism of action, apart from CD3 blockade, includes the induction of apoptosis in TL through a sustained stimulation of the TCR, while having no apparent effect of naïve T cells. Visilizumab has been tested in ulcerative colitis where it was not found effective and led to cardiovascular adverse events that have restricted the ulcer development of the drug, without any trials performed in SLE.

Other T cell depletion therapies. Here we can include an anti-CD7, a mouse anti-CD5 (CD5 Plus) and also a mouse-derived anti-CD4 (cM-T412) antibody, all of them T cell depletion, none tested in SLE.

Regulating T Cells

After antigenic stimulation, naïve T CD4 lymphocytes proliferate and differentiate, according to the local cytokine milieu, into different effector subtypes: Th1, Th2, Th17 or regulator T cells (Treg). Treg cells are characterized by the presence of CD4, CD25 and the FOXP3 transcription marker (T CD4+CD25+FOXP3+). These cells, partly corresponding to what was known as suppressor T cells, contribute to immune homeostasis and maintenance of peripheral tolerance, making the search for an agonistic action over them a possible therapeutic objective. In spite of there being several subpopulations within Treg, with functions that are still not properly profiled, at least 3 strategies exist to influence them agonistically.

Varinostat and entinostat (MS-275). Inhibitors of histone deacetylase, which induces the expression of FOXP3, a marker of Treg cells. It has been approved for use in skin lymphomas.

BT-061 (tregalizumab). The binding of the humanized monoclonal antibody tregalizumab to a single epitope od CD4 induces a Treg signaling pathway that leads to its activation; this agonistic effect on Treg showed some benefit and good tolerance in phase IIa trials on RA and psoriasis. It has not been tested in SLE.

Rapamycin (sirolimus, Rapamune®). A natural antibiotic used as a cytostatic due to its inhibiting effect on mTOR (mammalian
target of rapamycin), a fundamental regulator of cell growth and proliferation in many cell types. It has recently been observed that it up-regulates activation of CD4+ CD25+ FOXP3+ Tregs and, therefore, could represent a pathway to restore or increase suppressor T cell activity. In a small study carried out in 9 patients with SLE who had not responded to immunosuppressive treatment,13 rapamycin was administered and a reduction in disease activity (BILAG and SLEDAI) as in the use of steroids was seen. A wider prospective study is currently recruiting patients.

IL-2 (aldesleukina, Proleukin®). IL-2 is the main survivor factor in Treg cells; however, another of its effects, such as stimulating the production of TNF-α, IFN-γ and IL-6, does not make it an attractive target in SLE.

Another strategy using Treg has been the possibility of transfusions of previously extracted and expanded cells in vitro.

Cytokines

Multiple cytokines have been researched as therapeutic targets in SLE, with the aim of interrupting intercellular communication in different key steps of its pathophysiology.

Tumor Necrosis Factor Alpha

TNF-α has multiple proinflammatory effects that favor autoimmunity, but also has regulatory functions that may inhibit it. In fact, the fact that TNF can both enhance and weaken autoimmunity has been seen in different mouse models, so the use of TNF inhibitors in SLE may present with this same duality. In effect, in patient based studies, results are variable and seem to depend on time, with positive responses in the short but not in the medium-term. On the other hand, when TNF antagonists are used in RA, ANA becomes positive in up to half of cases, although drug induced lupus is present in less than 1%.14 A small study in 6 patients with LN or refractory lupus arthritis used infliximab (IFX, Remicade®) at 5 mg/kg in combination with azathioprine or methotrexate, leading to improvement of proteinuria and arthritis; although 4 patients showed an increase in anti-DNA and antiphospholipid antibodies, none presented worsening disease or thrombotic effects.15

Another study with IFX in renal lupus did not recruit the necessary number of patients and another, using etanercept (Enbrel®) was interrupted before it ended. There is a current trial with etanercept for discoid lupus underway.

Interleukin 6

IL-6 is a cytokine with multiple proinflammatory properties, of which stimulating plasma cells to produce antibodies is especially relevant for SLE, as it is promoting the differentiation of naïve T cells to Th17, which leads to the production of IL-17 and IL-10; another effect is the inhibition of naïve Treg cells by suppressing FOXP3, their characteristic marker. The inhibition of IL-6, as well as IL-17 and IL-10, in principle, should be a good therapeutic target in SLE.

Anti-IL-6r (tocilizumab, RoActemra®). A humanized monoclonal antibody against the soluble and membrane receptor of IL-6. It has been used in a small study with 16 patients in which it was effective but associated with a lot of infections;16 although most of them were mild and some did not require antibiotic, controlled studies are needed to estimate the real risk of infection with TCZ. No current efforts are being made with this drug.

A new generation of completely human monoclonal antibodies vs IL-6r (REGN88, SAR153191) is in its first stages of development.

Anti-IL-6 (ALDS18). A humanized monoclonal antibody vs IL-6, in which a phase II trial involving 132 patients with RA, but not SLE, has been carried out.

Interleukin 17

IL-17, which includes 6 members called IL-17A to IL-17F, is a proinflammatory cytokine with, among other functions, the participation in immune responses against extracellular bacteria and fungi, and activating the production of chemokines (CK) on the part of neighboring cells, which then recruit monocytes and neutrophils. IL-17 is abnormally elevated in SLE. Th17 cells are implicated in this hyperproduction, as in differentiation of T CD4+ cells in the presence of TGF-β (transforming growth factor β) and other cytokines, such as IL-6, IL-21 and IL-23. Other cell elements that contribute to a greater generation of Th17 are PDCs, through cytokines such as IL-6 and IL-23, and T cells, which infiltrate disease affected organs such as the skin or kidney.18 Elevated IL-17, in addition to its proinflammatory effect, has another effect in SK: stimulation of B cells, therefore increasing autoantibody titers. This group of functions produces a vicious cycle in which high IL-17 activates innate immune system cells, such as PDC, the local action of IL-17 in the affected organs generates more autoantigens from damaged cells and this produces more immune complexes after the greater production of autoantibodies to which IL-17 has contributed.19 Antibodies vs IL-17A and its receptor are being tested for RA and psoriasis.

Secukinumab (AIN457). Human anti-IL17A tested in RA, psoriasis and uveitis,20 but not in SLE. There is currently one trial evaluating efficacy and safety of secukinumab in RA patients who did not tolerate or had an inadequate response to anti-TNF.

LY2439821. Anti IL-17 humanized monoclonal antibody, used in RA.21

Interleukin 10

IL-10 is a mainly anti-inflammatory cytokine with a potent suppressive effect on APC and IL, inhibiting the synthesis of inflammatory cytokines, secretion of CK and expression of costimulation molecules such as CD80 and CD86, all of which would lead to attenuation of autoimmunity. However, in certain circumstances, IL-10 might have proinflammatory effects, promoting proliferation, differentiation and production of antibodies on the part of BL. In fact, patients with SLE show abnormally high levels of IL-10 correlating with disease activity and, in mouse models, accelerating the development of nephritis, while anti-IL-10 treatment delays it. It has recently been proven that the presence of IC and IFN-α, both abundant in SLE, reduce the anti-inflammatory capacity of IL-10, explaining this cytokines paradoxical behavior in SLE.22

Anti-IL-10 (B-N10). Attempting to answer this question, a small group of 6 patients with active SLE and dependent on steroids received a murine monoclonal anti-IL-10 (B-N10), showing a decrease in disease activity up to 6 months after a 21-day administration;23 with all patients developing anti-B-N10 antibodies. Phase I trials with a human monoclonal anti-IL-10 antibody are in the works.

Interleukins 12 and 23

IL-12 and IL-23 are secreted by macrophages and dendritic cells and intervene in the differentiation of R cells: IL-12 is composed by the p35 and p40 subunits, and induces Th1 lymphocytes, while IL-23 has the same p40 subunit and another subunit, p19, and contributes to Th17 differentiation.

Ustekinumab (CTO 1275, anti-p40). In mouse models it has been seen that animals lacking p40 are protected against arthritis, so a human antibody against this subunit has been developed, showing efficacy and safety in inflammatory intestinal disease,24 psoriasis and psoriatic arthritis.
Interleukin 21

IL-21 is a key molecule in differentiation of T lymphocytes toward an IL-17 inflammatory secretion pattern. In addition, IL-21 plasma levels in lupus patients are elevated compared to controls and in vitro studies show an increased proportion of IL-21+ T cells, correlated with the proportion of IL17+ T cells. In the BXSB-Yaa mouse model, the knockouts for the IL-21 receptor (IL-21R) developed an attenuated form of lupus. In addition, IL-21 has a potent effect on B cell proliferation and differentiation to plasma cells. Along with these effects, which support a therapeutic agonist of IL-21, we know that this cytokine has a proapoptotic effect on naïve B cells, making it difficult to predict the effect of a molecule regarding its net balance of inhibition in autoimmune diseases and which has not been tested in SLE yet.

Mitogen-Activated Protein Kinases

These mediate cell activities that include proliferation, survival/apoptosis and production of cytokines and metalloproteases. p38 is the best characterized and intervenes in the production of inflammatory cytokines, such as TNF-α, IL-1β and IL-6, as well as synthesize CK. Studies carried out with inhibitors of p38 (pamapimod, SCIO-460, VX-702) in RA have shown modest benefit and considerable toxicity. These results seem to be poor because p38 loss its function downstream and the signaling pathway may be easily redirected to more proximal points through other kinases.

Tyrosine Kinases

Spleen tyrosine kinase (Syk) is an important mediator of signaling related to Fc receptor activation, making it a potential target in SLE because, at least in part, T cell autoreactivity in this disease is due to an anomalous stimulation of the TCR-CD3 complex and, on the other hand, a study on the efficacy in RA of fostamatinib, a SyK inhibitor, observed an early reduction in IL-6 levels. Fostamatinib (R788). A prodrug that, after oral administration, converts into R406, a potent SyK inhibitor. RA trials have contradictory results30,31 and additional studies are needed to establish their usefulness in SLE.

Imatinib (Gleevec®). BCR-ABL tyrosine kinase inhibitor, used in chronic myeloid leukemia, with positive effect in animal models of autoimmunity, such as diabetes in NOD (non obese diabetic) mice or collagen induced arthritis. This has led to renewed interest in this molecule and it is currently being tested in type 1 diabetes, MS and RA.

Janus Kinases

JAK1, JAK2, JAK3 and Tyk2, from the tyrosine kinase family of STAT (signal transducer and activator of transcription) transcription factors, integrate the JAK–STAT system that transduces signals from almost 40 cytokines and growth factors. JAK3 is critical for intracellular signal transduction from receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, ending in the activation of STAT proteins, which travel to the nucleus and mediate gene transcription. These cytokines intervene in lymphocyte activation and its suppression might lead to beneficial effects on autoimmune diseases.

Tofacitinib (tasocitinib, CP-690 550). A JAK3 inhibitor that has demonstrated its clinical efficacy in a phase II trial of RA patients with good ACR responses. Another phase II/III open label study showed a reduction in DAS28 as well as improvement in the ACR response. In both, infections due to neutropenia were the most frequent adverse event.

Nuclear Factor κB

A protein complex in charge of cell responses that controls DNA transcription, it is involved in reactions to stress, cytokines, free radicals and viral and bacterial antigens. No inhibitor molecules for these proteins have been tested in SLE.

Other Intracellular Targets

Tacrolimus (FK 506). Is a calcineurin inhibitor that leads to alterations in calcium flux. In animal models it reduces the incidence of skin lesions and has been proposed as an alternative for topical steroids in cutaneous lupus, but controlled studies are needed because the few available ones include few patients or lack a control group.

Seliciclib (CYC202). CDK (cyclin-dependent kinases) is a family of cell cycle-regulating protein kinases. Seliciclib stops the cell
cycle by inhibiting these proteins and is being tested in patients with solid tumors and B cell lymphomas. In mouse SLE models it delays the appearance of proteinuria, reduces the production of anti-dsDNA antibodies and prolongs survival.\textsuperscript{35} Inhibition of these proteins could represent an attractive route for the treatment of SLE.

Laquinimod. An oral quinolone carboxamide, it has been effective in several models of autoimmune disease, including lupus. Its target is unknown, but it is considered an immune modulator with an action dependent of the Th1/Th2 balance, resulting in an inhibition of proinflammatory cytokines and an increase in anti-inflammatory ones.\textsuperscript{36} Microarrays studies in patients with MS showed that laquinimod induces suppression of antigen presentation related genes; these effects were fundamentally found in the NFκB signaling pathway. Laquinimod has been used fundamentally for MS and is currently being tested in active LN.\textsuperscript{37}

Proteasome Inhibitors

The proteasome is a complex structure in charge of proteolysis, the degradation of proteins which are damage or obsolete. Ubiquitin is crucial in this process, marking proteins to be degraded so that they can be recognized by the proteasome. While most cells in the organism express a conventional proteasome (constitutive proteasome or subunit B5), cells of the immune system express a particular proteasome (subunit LMP7) called immunoproteasome. Inhibition of the proteasome leads to apoptosis due to the interruption of the degradation of key proteins in the cell cycle; additionally, antigens bound by APCs are peptides produced by degradation by proteasomes, therefore it collaborates indirectly with TL antigen-presenting. On the other hand, the immunoproteasome regulates the production of different proinflammatory cytokines, such as TNF, IL-6 and IL-23, and inhibition of the proteasome has an especially intense effect mainly on plasma cells, with its current clinical application centered on myeloma. However, advantages over the synthesis of autoantibodies in autoimmune inflammatory diseases could derive from these effects. There are currently 2 non-specific or dual (inhibiting both types) proteasome inhibitors (bortezomib and carfilzomib) and an immunoproteasome-specific inhibitor (ONX 0914).

Carfilzomib y bortezomib (Velcade\textsuperscript{®}). Non-specific proteasome reversible inhibitors. They are used for treatment of myeloma, but their effect is limited because it produces peripheral neuropathy with a certain frequency. Both these and ONX 0914 have been tested in SLE mouse models, demonstrating a prevention in the development of disease and a reduction in the synthesis of antibodies by a double mechanism that includes the reduction of the number of plasma cells and the suppression in the production of IFN-α by PDC.\textsuperscript{38} Both effects that make proteasome inhibitors extraordinarily interesting molecules for the treatment of SLE.

Ethical Responsibilities

Protection of Human and Animal Subjects. The authors declare that the procedures followed conformed to the ethical norms of the human experimentation committee and were in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of Data. The authors declare that no patient data appear in this article.

Right to Privacy and Informed Consent. The authors declare that no patient data appear in this article.

Conflict of Interest

Antonio C. Zea Mendoza is the PI of clinical trials for Abbott Lab, MSD, Astra-Zeneca and UCB Pharma.

Alina L. Boteanu collaborates in a clinical trial with Astra-Zeneca. Walter A. Sifuentes Giraldo, María J. García Villanueva and Ana Loís Iglesias have no disclosures to make.

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