Reumatol Clin. 2012;8(5):263–269

Reumatología Clínica

www.reumatologiaclinica.org

Review Article

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

Walter A. Sifuentes Giraldo, María J. García Villanueva, Alina L. Boteanu, Ana Lois Iglesias, Antonio C. Zea Mendoza*

Servicio de Reumatología, Hospital Universitario Ramón y Cajal, Madrid, Spain

ARTICLE INFO

Article history:
Received 26 December 2011
Accepted 4 January 2012
Available online 19 September 2012

Keywords:
Systemic lupus erythematosus
Pathogenesis
Treatment
Biological therapies

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.

© 2011 Elsevier España, S.L. All rights reserved.

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

Palabras clave:
Lupus eritematoso sistémico
Patogenia
Tratamiento
Terapias biológicas

RESUMEN

Glucocorticoides, aspirina, antipalúdicos 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.

© 2011 Elsevier España, S.L. Todos los derechos reservados.

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 placebo[2]; however, a second,

☆ Please cite this article as: Sifuentes Giraldo WA, et al. Nuevas dianas terapéuticas en el lupus sistémico (parte 2/2). Reumatol Clin. 2012;8(5):263–9.

* Corresponding author.
E-mail address: azea.hrc@salud.madrid.org (A.C. Zea Mendoza).

2173-5743/$ – see front matter © 2011 Elsevier España, S.L. All rights reserved.

post hoc analysis that excluded patients with negative ANA and found a new response index, SRI (SLE response index)—defined by an improvement ≥4 points on the SLEDAI, no new BILAG 1A/2B and no worsening of the global evaluation by the physician—established that patients with positive ANA SLE treated with standard therapy plus belimumab for 5 years had a sustained improvement of SLE, a reduction in the frequency of flares (including severe flares) 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 in immunologic parameters, normalization of hypergammaglobulinemia and a significant reduction on autoantibodies. This led to its approval by the FDA in March 2011 as a treatment for SLE in combination with standard therapy, thus becoming the first drug approved for the treatment of this disease since 1957.[3]

Briobacept (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 subpopulations: $CD21^{high}$, 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-IgG is a recombinant fusion protein that simulates 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 having a comfortable subcutaneous weekly administration.[4] A phase II clinical 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 (blisimimod). Is a *peptibody* (a hybrid of a small peptide 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 "inflammatory" 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 (TGN1412). 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 multiorganic failure, a phenomenon 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 BILAG A or B a to only a new BILAG 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 abatacept, 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, dendritic 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, toralizumab and ABI 793.

Ruplizumab (BG9588). It was in a small trial with 28 LN type IV patients, interrupted due to a high incidence of thromboembolic 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 C_3.[8]

Toralizumab (IDEC-131, E6040, anti-gp39). A clinical trial of toralizumab vs placebo in mild to moderate SLE found no thromboembolic events but neither did it find clinical efficacy.[9] The

Download English Version:

https://daneshyari.com/en/article/3384474

Download Persian Version:

https://daneshyari.com/article/3384474

Daneshyari.com