13

The Emerging Role of Monoclonal Antibodies in the Treatmentof Systemic Lupus Erythematosus

Ewa Robak and Tadeusz Robak
Medical University of Lodz
Poland

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by B cell hyperactivity and defective T-cell function, with production of high titer autoantibodies and clinical involvement in multiple organ systems. Patients with mild SLE can generally be maintained on a combination of non-steroidal anti-inflammatory drugs and antimalarials. Corticosteroids, azathioprine and cyclophosphamide remain important for long term management of most patients with active disease and even those in clinical remission. However, these agents have considerable side effects and are not effective in all patients with SLE. Novel immunological therapies include both B and T cell directed treatments, anticytokine and complement directed therapies. These modalities enable more specific immunosuppression, and include cyclosporin, high-dose intravenous immunoglobulin, mycophenolate mofetil, tacrolimus and new purine nucleoside analogs (Schröder and Zeunerorts 2009).

In recent years, clinical studies have been undertaken with selected monoclonal antibodies (mAbs) in the treatment of several hematological diseases, especially in malignant disorders. However, some clinical observations indicate that mAbs may be an important alternative for the conventional therapy of some autoimmune disorders (Robak 2004).

B-lymphocytes are an essential component of the acquired immune response (La Cava 2010). They randomly express cell-surface receptors which are often autoreactive and must be controlled by the process of B-cell tolerance. In SLE, the number of B-cells in the peripheral blood is often decreased, and those that are present have abnormal phenotypes indicative of activation. The important role of B cells in the pathogenesis of SLE has provided a strong rationale to target B cells in SLE. Selective therapeutic depletion of B-cells became possible with the availability of the anti-CD20 antibody rituximab.

2. Anti-CD20 monoclonal antibodies

The CD20 (B1) antigen is a 33–35 kDa integral membrane protein expressed on the surfaces of non-malignant and most malignant B cells (Cragg, Walshe et al. 2005). The CD20 protein consists of cytoplasmic N- and C-termini and four hydrophobic regions for anchoring the molecule in the membrane (Robak 2008). The characteristics that make CD20 a good target

antigen include its relatively high level of expression and close location of the extracellular epitopes to the cell surface. The intensity of antigen expression or the number of receptor sites on the cell surface appears to correlate with the clinical response. The cytotoxic activity of mAbs directed against CD20+ cells is thought to be based on antibody-dependent cellular cytotoxicity (ADCC) via natural killer (NK) cell responses, complement-dependent cytotoxicity (CDC), or by the induction of cell signaling followed by apoptosis. At present, rituximab is the most important mAb of clinical value in patients with autoimmune disorders and B-cell lymphoid malignancies. Over the last few years, new generations of anti-CD20 mAbs have been developed for potential benefits over rituximab (Robak and Robak 2011; Lim, Beers et al. 2010). They were engineered to have augmented antitumor activity by increasing CDC or ADCC activity and increased Fc binding affinity for the low-affinity variants of the FcγRIIIa receptor (CD16) on immune effector cells. The second-generation mAbs are humanized or fully human to reduce immunogenicity, but with an unmodified Fc region. They include ofatumumab, veltuzumab, and ocrelizumab. The third-generation mAbs are also humanized but in comparison with the second-generation mAbs they also have an engineered Fc region designed to increase their effector functions by increasing binding affinity for the FcγRIIIa receptor (Ruuls, Lammerts et al. 2008). Both polymorphisms in FcγRIIIa and structure of mAb Fc can impact on the affinity between FcγRIIIa and mAb. The third-generation mAbs include AME133v, Pro13192, and GA-101.

2.1 Rituximab

Rituximab is an IgG-1κ immunoglobulin, containing murine light– and heavy–chain variable–region sequences and human constant region sequences. Rituximab is known as the first-generation mAb. Since approval in 1997, rituximab has become the standard of care in follicular B-cell lymphomas (FL), CLL, and aggressive lymphomas when combined with chemotherapy (Hauptrock and Hess 2008). Rituximab is administered as an intravenous infusion with a recommended dosage of 375 mg/m^2 given once weekly for 4 weeks. Treatment with this agent is usually well tolerated. However, infusion-related reactions occur in the majority of patients. These adverse events are typically fever, chills, rigors and rare hypotension and bronchospasm, although the incidence of these side effects decreases with subsequent rituximab infusion. Moreover, prolonged impairment of antibody production causes the increased risk of viral and bacterial infections. It should be also remembered that rituximab is a human mouse chimeric antibody and hence treated patients may be susceptible to the development of human antichimeric antibodies, which can impact on responsiveness.

A recent study has shown that treatment with rituximab affects both the cellular and humoral arm of the immune system in patients with SLE (Lu, Ng et al. 2009).

A number of prospective studies and several retrospective cohort studies of rituximab in the treatment of SLE have been reported (Cambridge, Isenbergetal. 2008). In 2005 Leonardo et al. (Leandro, Cambridge et al. 2005) described female patients with SLE who were treated with combination of rituximab, CY and prednisolone. Each patient received two infusions of rituximab (500 mg/dose), two infusions of cyclophosphamide (750 mg/dose) and 60 mg prednisolone per day for five days. Five patients were analyzed and one patient was lost to follow up after 3 months. All five patients showed an improvement in British Isles Lupus Assessment Group (BILAG) scores from a median of 14 at baseline to a median of 6 at six months. Recently, the same group reported the results of 46 patients with active SLE were

treated with a 1 gm of rituximab, 750 mg of cyclophosphamide, and 100-250 mg of methylprednisolone, administered on 2 occasions 2 weeks apart (Lu, Ng et al. 2009). Twenty one patients (47%) reached partial remission after one cycle (mean followup 39.6 months). Treatment resulted in a decrease in median global BILAG scores from 12 to 5 ($P < 0.0001$) and median anti-double-stranded DNA antibody titers from 106 to 42 IU/ml ($P < 0.0001$). In addition an increase in the median C3 level from 0.81 to 0.95 mg/liter ($P < 0.02$) at 6 months was observed. Five serious adverse events were noted.

Willems et al. (Willems, Haddad et al. 2006) described the safety and efficacy of rituximab in 11 girls (mean age 13.9 years) with severe SLE including 8 girls with class IV or V lupus nephritis, 2 girls with severe autoimmune cytopenia and 1 girl with an antiprothrombin antibody. Patients received 2 to 12 intravenous infusions of rituximab (350-450 mg/m^2/ infusion) with corticosteroids. Remission was achieved in 6 of 8 patients with lupus nephritis and in two patients with autoimmune cytopenia. However, severe adverse events occurred in 45% of the patients in this study.

Looney et al. reported the results of the first dose escalation study of rituximab for the treatment of SLE (Looney, Anolik et al. 2004). The drug was added to ongoing therapy in 18 patients with moderately active SLE. Six patients received a single infusion of 100 mg/m^2, six received one infusion of 375 mg/m^2 and six patients received four weekly doses of 375 mg/m^2. In this study, rituximab-induced B cell depletion was translated into a significant improvement in SLE disease activity even in the absence of substantial serologic responses. Most patients were able to decrease corticosteroid dose from 13 to 10 mg by the end of the study and three patients were able to discontinue concomitant immunosuppressives. The clinical response was most notable for rashes and arthritis.

Terrier et al. analyzed recently prospective data from the French AutoImmunity and Rituximab (AIR) registry, which includes data on patients with autoimmune disorders treated with rituximb (Terrier, Amoura et al. 2010). Overall response was observed in 80 of 113 patients (71%) by the SELENA-SLEDAI (SLE Disease Activity Index Score assessment). Efficacy was similar between patients receiving rituximab monotherapy and those receiving concomitant immunosuppressive agents. Articular, cutaneous, renal, and hematologic improvements were noted in 72%, 70%, 74%, and 88% of patients, respectively. In relapsed patients response was observed in 91% after retreatment with rituximab. Severe infections were observed in 12 patients (9%), corresponding to a rate of 6.6/100 patient-years. Most severe infections occurred within the first 3 months after the last rituximab infusion. Five patients died, due to severe infection (n = 3) or refractory autoimmune disease (n = 2).

Merrill et al reported the results of the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial, a placebo-controlled, double-blind, multicenter study of rituximab in patients with moderately-to-severely active extrarenal SLE (Merrill, Neuwelt et al. 2010). Patients were randomized at a 2:1 ratio to receive intravenous rituximab (1,000-mg) or placebo on days 1, 15, 168, and 182, which was added to prednisone. Of the 257 patients, 88 were assigned to receive placebo, and 169 were randomized to the rituximab arm. At week 52, no difference was observed in major clinical responses or partial clinical responses between the placebo group. Decreases in the level of anti-dsDNA autoantibodies and increases in complement C3 and C4 levels were greater in the rituximab group than in the placebo group. The overall response rate was 28.4% and 29.6%, respectively. The proportion of patients in whom serious infection developed was 17% in the placebo group and 9.5% in the rituximab group.

Rituximab is also an active treatment agent in patients with lupus nephritis and central nervous system (CNS) involvement. Sfikakis et al. reported clinical response in 80% and sustained complete response in 40% of patients with class III and IV nephritis treated with rituximab and moderate doses of corticosteroids (Sfikakis, Boletis et al. 2005). In the study of Ng et al. 21 patients with renal involvement were treated with rituximab and cyclophosphamide (Ng, Cambridge et al. 2007). They had a decrease in median urinary protein creatinine ratio (PCR) from 446 to 190 mg/mmol 6 months. More recently, Pepper et al. treated 18 patients with class III/IV/V lupus nephritis with rituximab. All patients were on steroids prior to the development of lupus nephritis (Pepper, Griffith et al. 2009). The patients received mycophenolate mofetil maintenance therapy. Fourteen of 18 patients achieved complete or partial remission with a sustained response of 67% at 1 year. In addition, serum albumin increased from a mean of 29 g/L at presentation to 34 g/L at 1 year ($P = 0.001$). Importantly, following treatment with rituximab, 6 patients stopped prednisolone, 6 patients reduced their maintenance dose and 6 patients remained on the same dose (maximum 10 mg). No severe infections were observed.

The study performed by Tokunaga et al. showed marked improvement following rituximab therapy in patients with neuropsychiatric SLE (Tokunaga, Saito et al. 2007). A monoclonal antibody was administered at doses of 375 mg/m^2 once weekly for four weeks or 1000 mg once weekly for two weeks in 10 patients with refractory neuropsychiatric SLE. Treatment resulted in rapid improvement of CNS–related manifestations, particularly acute confusional state. Rituximab also improved cognitive dysfunction psychosis and seizure and reduced the SLEDAI on day 28 in all 10 patients. These effects lasted for more than a year in 5 patients. In another study, Smith et al. (Smith, Jones et al. 2006) evaluated prospectively the effects of rituximab treatment for refractory SLE and vasculitis. Patients received four weekly infusions of rituximab at a dose of 375 mg/m^2. Intravenous cyclophosphamide (500 mg) was administered along with the first infusion in an effort to achieve early disease control. Remission followeing rapid B cell depletion was achieved in all 11 patients including 6 complete responses and 5 partial responses. Moreover, a renal response occurred in all 6 patients with lupus nephritis. Clinical improvement was accompanied by a significant reduction in the daily dose of prednisone. Seven of 11 patients experienced a relapse, a median of 12 months after treatment. After relapse, six patients with SLE were re-treated with rituximab and all achieved remission and did so more quickly than after the primary treatment.

Rituximab is generally well tolerated. Even fewer adverse events have been observed in patients treated for SLE than in the lymphoma patients (Tokunaga, Saito et al. 2007). The most common adverse events during or following rituximab therapy are infusion related symptoms, typically fever, chills, rigors and hypotension. In patients who receive premedication consisting of antipyretic and antihistaminic drugs together with corticosteroids, infusion-related side effects are usually only mild or moderate and do not require discontinuation of rituximab administration. Occasionally, serious infections were also reported. However, these may have been related to the underlying disease and/or concomitant therapy with other immunosuppressive agents. In 2006, an FDA alert was reported after two SLE patients treated with rituximab had died from progressive multifocal leukoencephalopathy (PML) (Ermann and Bermas 2007). However, both patients had received additional treatment with cyclophosphamide. At present, it is difficult to estimate the risk of this complication in SLE patients treated with rituximab. In recent analysis, among the rheumatic diseases, 43 cases of PML (0.44%) were associated with SLE, 24 (0.25%)

with rheumatoid arthritis (RA), and 25 (0.26%) with other connective tissue diseases (CTDs) (Molloy and Calabrese 2009). Additional controlled studies with new designs are needed to define the place of rituximab in the therapeutic arsenal for SLE.

2.2 New generations of Anti-CD20 monoclonal antibodies

Over the last few years, new generations of anti-CD20 monoclonal antibodies have been developed for potential benefits over the classical, first-generation mAb rituximab. Compared with rituximab, new mAbs have enhanced antitumor activity resulting from increased CDC and ADCC, and increased Fc binding affinity for the low-affinity variants of the FcγRIIIa receptor (CD16) on immune effector cells (Czuczman & Gregory 2010).

2.2.1 Ofatumumab

Ofatumumab (HuMax-CD20; Arzerra™, GlaxoSmithKline plc/Genmab A/S) is a second-generation, fully human, anti-CD20, IgG1 mAb in phase I, II and III trials for hematological malignancies and autoimmune diseases such as rheumatoid arthritis (RA) and multiple sclerosis. Ofatumumab specifically recognizes an epitope encompassing both the small and large extracellular loops of CD20 molecule, and is more effective than rituximab at CDC induction and killing target cells. In April 2010, the European Medicines Agency granted a conditional marketing authorization for ofatumumab, for the treatment of fludarabine-refractory CLL patients. It has been reported recently that ofatumumab, administered as 2 i.v. infusions at doses 300 mg, 700 mg, or 1,000 mg is clinically effective in patients with active RA (Østergaard , Baslund et al. 2010). Rapid and sustained peripheral B cell depletion was noted in all dose groups. Overall, 70% of patients receiving ofatumumab had a moderate or good response according to the European League Against Rheumatism (EULAR) criteria at week 24.

2.2.2 Veltuzumab

Veltuzumab (IMMU-106, hA20; Immunomedics Inc., Morris Plains, NJ) is a second-generation, type 1, humanized, anti-CD20, IgG1 mAb with complementarity-determining regions (CDRs) similar to rituximab (Goldenberg, Rossi et al. 2009). This mAb is generated using the same human immunoglobulin as epratuzumab and has a >90% humanized framework. It is also very similar to rituximab in terms of antigen binding, specificity binding, and dissociation constant. Veltuzumab differs from rituximab by one amino acid (Asp101 instead of Asn101) in the CDR 3 of the variable heavy chain. Smaller murine regions may reduce infusion reactions, infusion times, and immunogenicity. This antibody has enhanced binding avidities and a stronger effect on CDC compared with rituximab in selected cell lines. Veltuzumab is safe and active agent in NHL. B cells were depleted after the first infusion of all tested doses, including dose levels less than those typically used with rituximab (Morschhauser, Leonard et al. 2009).

2.2.3 Ocrelizumab

Ocrelizumab (Genentech Inc/Biogen Idec Inc/Chugai Pharmaceutical Co Ltd/Roche Holding Ag) is a second-generation, type 1, humanized, anti-CD20, IgG1 mAb with modifications of the Fc region that lead to enhanced ADCC and reduced CDC activities compared with rituximab (Kausar, Mustafa et al. 2009).This agent has the potential for enhanced efficacy compared with rituximab due to increased binding affinity for the low-

affinity variants of the FcγRIIIa receptor on immune effector cells (Genovese, Kaine et al. 2008). Ocrelizumab binds to a different, but overlapping, epitope of the extracellular domain of CD20 as compared with rituximab. Ocrelizumab is a humanized mAb with the potential for enhanced efficacy in lymphoid malignancies compared with rituximab due to increased binding affinity for the low-affinity variants of the FcγRIIIa receptor (Faria & Isenberg 2010).

2.2.4 GA-101

GA-101 (RO5072759) is a fully humanized, type II, IgG1 mAb derived from humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering using GlycoMab® technology. GA-101 was designed for enhanced ADCC and superior direct cell-killing properties, in comparison with currently available type I antibodies (Robak 2009). In contrast to rituximab GA101, mediated significant NK cell degranulation in whole blood samples. Thus, CDC and ADCC are believed to be the major effector mechanisms of GA101 in whole blood assays (Bologna, Gotti et al. 2011).

2.2.5 TRU-015

TRU-015 (CytoxB20G, Trubion Pharmaceuticals Inc and Pfizer Inc) is a small modular immunopharmaceutical (SMIP) derived from key domains of an anti-CD20 antibody. TRU-015 represents a novel biological compound that retains Fc-mediated effector functions and is smaller than mAbs (Rubbert-Roth 2010). SMIPs belong to a novel proprietary biologic compound class that retain Fc-mediated effector functions and are smaller than mAbs (Robak, Robak et al. 2009). A SMIP molecule is a single-chain polypeptide consisting of one binding domain, one hinge domain, and one effector domain. The TRU-015 SMIP molecule is the homogeneous single-chain immunotherapeutic derived from key domains of an anti-CD20 antibody, for the potential intravenous infusion treatment of RA, SLE and B-cell lymphoid malignancies (Hayden-Ledbetter, Cerveny et al. 2009). This molecule is a compact dimer of 104 kDa that co-migrates with albumin in size exclusion chromatography and retains a long half-life *in vivo*. It is effective in mediating target cell killing in the mechanism of ADCC but has reduced CDC activity compared with rituximab. TRU-015 could represent a novel therapy for the treatment of SLE, although the efficacy, safety profile, and advantages of this compound compared with existing therapeutic options would need to be established in clinical trials (Burge, Bookbinder et al. 2008). TRU-015 has shown clinical efficacy and tolerability in phase IIa and IIb studies in patients with rheumatoid arthritis, and clinical development efforts for the treatment of lymphoma and inflammatory disease are ongoing. In the ongoing trial pharmacokinetics of TRU-015 after a single administration in subjects with membranous nephropathy secondary SLE is investigated (ClinicalTrials.gov Identifier: NCT00479622).

All new anti-CD20 mAbs are potentially useful in the treatment of SLE. However, the advantage of these new drugs over rituximab should be proven by well-designed clinical trials in rituximab-refractory patients or through head-to-head comparison.

3. Other B cell targeting monoclonal antibodies

3.1 Anti-CD22 antibody epratuzumab

Epratuzumab (Immunomedics, Inc.) is a humanized monoclonal IgG antibody that specifically targets the CD22 antigen on B cells (Leonard & Goldenberg 2007). This

monoclonal antibody is 90% to 95% of human origin thus greatly reducing the potential for immunogenicity. Unconjugated anti-CD22 antibodies only partially deplete B cells, but might deliver a negative signal by binding CD22 to the cell surface (Daridon, Blassfeld et al. 2010). Treatment of SLE patients with epratuzumab leads to a reduction of circulating CD27 negative B-cells, although epratuzumab is weakly cytotoxic to B-cells *in vitro*. Epratuzumab binding was higher on B-cells relative to T-cells. In addition, weak non-specific binding of epratuzumab on monocytes was noted. On B-cells, binding of epratuzumab was enhanced on CD27negative B-cells compared to CD27 positive B-cells, primarily related to a higher expression of CD22 on CD27negative B-cells. Epratuzumab also enhanced the migration of CD27negative B-cells towards the chemokine CXCL12.

Recently, Dorner et al. reported the results of an open-label, single-center study of 14 patients with moderately active SLE (Dörner, Kaufmann et al. 2006). Patients received 360 mg/m^2 of epratuzumab intravenously every 2 weeks for 4 doses with analgesic antihistamine premedication prior to each dose. Total BILAG scores decreased by ≥50% in all 14 patients at some point during the study with 92% having decrease in various amounts continuing to at least 18 weeks.

Epratuzumab toxicity consisted primarily of mild to moderate transient infusion–related events during the first infusion. These results support conducting multicenter controlled studies to examine the effects of epratuzumab in broader patient populations. A U.S. patent has been issued to Immunomedics, Inc. for epratuzumab as a potential new treatment for lupus.

3.2 Anti-BlyS monoclonal antibodies

The B-lymphocyte Stimulator (BLyS) and A Proliferatiave Inducing Ligand (APRIL) are ligands for receptors BAFF-R (B Cell Activation Factor), BCMA (B Cell Maturation Associate) and TACI (Transmembrane Activator and Calcium Reproducing Initiator). BLyS also known as BAFF, THANK, TALL-1 or zTNF4, is a member of TNF super-family, which stimulates immunoglobulin (Ig) production by binding to specific receptors (King and Hahn 2007). In patients with SLE, the serum levels of BLyS are elevated and its neutralization has suggested that higher levels of BLyS contribute to the generation of autoantibodies and is important in SLE pathogenesis (Toubi, Kessel et al. 2006). In consequence, neutralization of BLyS may play a role in the therapy of this disease.

3.2.1 Belimumab

Belimumab (Human Genome Sciences, (Rockville, MD, USA)/Glaxo Smith Kline, (Uxbridge, UK)) is a fully human IgG1 mAb that specifically binds and inhibits the biological activity of BLyS (Wiglesworth, Ennis et al. 2010). The antibody exerts its biological activity by preventing the binding of BLyS to its receptors, resulting in autoreactive B cell apoptosis (Baker, Edwards et al. 2003). It also inhibits soluble BLyS activity at subnanomolar concentrations in a murine model. Belimumab inhibits also BLyS- induced proliferation of B-cells *in vitro* and prevents human BLyS-induced increases in splenic B-cell numbers and serum IgA titers in mice.

The safety, tolerability, immunogenicity, and pharmacology of belimumab were investigated in a phase I, randomized, placebo controlled, double-blind study in patients with SLE (Furie, Stohl et al. 2008). Seventy patients with mild to moderate disease were enrolled in this trial. Fifty-seven patients were treated with mAb and 13 with placebo. The drug was administered at 4 different doses (1.0, 4.0, 10 and 20 mg/kg) as single infusions, 21

days apart. The incidence of adverse events and laboratory abnormalities was similar among the belimumab and placebo groups. A significant reduction in the median percentage of CD20+ B-cells was noted with a one and two doses of belimumab versus placebo. However, SLE activity did not change after treatment with this mAb.

Wallace et al. assessed the safety, tolerability, biological activity, and efficacy of belimumab in combination with standard of care therapy in patients with active SLE (Wallace, Stohl et al. 2009). In this phase II, randomized trial 449 patients with SELENA-SLEDAI score ≥ 4 were randomly assigned to belimumab (1, 4, 10 mg/kg) or placebo in a 52-week study. In this study, belimumab treatment did not result in significant improvement compared with placebo. Percentage change in the SELENA-SLEDAI score at week 24, the primary endpoint of the study, was similar in both arms (19.5% in the belimumab group versus 17.2% in the placebo group). There was no significant difference in time to first SFI-defined flare over 52 weeks between the belimumab and placebo groups (67 versus 83 days, respectively). However, the median time to first SLE flare during weeks 24–52 was significantly longer with belimumab treatment (154 versus 108 days; P=0.0361). During the 52-week study and 8-week follow-up period, the incidence of AEs were similar in all treatment groups, including placebo. Only urticaria was statistically more frequent in belimumab-treated patients (4% versus 0%).

The efficacy and safety of belimumab in patients with active SLE was also assessed in a large, randomized, multicenter study recently reported by Navarra et al 2011 (Navarra, Guzmán et al. 2011). In this trial, 865 patients with scores of at least 6 on the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) were randomly assigned to belimumab 1 mg/kg or 10 mg/kg, or placebo by intravenous infusion in 1 h on days 0, 14, and 28, and then every 28 days until 48 weeks, with standard of care. Significantly higher Systemic Lupus Erythematosus Responder Index (SRI) rates were noted with belimumab 1 mg/kg (51%, P=0.0129) and 10 mg/kg (58%, p=0.006) than with placebo (44%) at week 52. In addition, more patients had SELENA-SLEDAI score reduced by at least 4 points during 52 weeks with belimumab 1 mg/kg (53%, P=0.0189) and 10 mg/kg (58%, P=0.0024) than with placebo (46%). Moreover, more patients receiving belimumab 1 mg/kg (78%, P=0.1064) and 10 mg/kg (81%, P=0.0181) had no new BILAG A or no more than 1 new B flare than did those receiving placebo (73%). There was no difference in rates of adverse events in patients given belimumab 1 mg/kg and 10 mg/kg, and placebo. Serious infection was noted in 8%, 4%, and 6% patients, respectively. Severe or serious hypersensitivity reactions on an infusion day were reported in four patients.

3.2.2 LY2127399

Anti-BAFF monoclonal antibody LY2127399 (Eli Lilly & Company Limited) is a fully human IgG4 antibody with neutralizing activity against both membrane-bound and soluble BAFF. This may reduce the activity, proliferation and survival of B-cells. The ongoing study evaluates the efficacy, safety and tolerability of two different doses of LY2127399 administered in addition to standard of care therapy in patients with active SLE (ClinicalTrials.gov Identifier: NCT01205438).

4. Monoclonal antibodies inhibiting T cell costimulation

Cytotoxic lymphocyte-associated antigen-4 (CTLA-4) is a potent inhibitor of the costimulation pathway necessary to activate T cells. Abatacept (CTLA-4 immunoglobulin; CTLA4-Ig,

Orencia) is a recombinant fully humanized fusion protein, composed of the extracellular domain of human CTLA-4 and a modified Fc part of IgG-1that was engineered to prevent complement fixation (St Clair 2009). It targets T cell activation by interfering with one of the costimulatory mechanisms that are essential for cell activation. CTLA4-Ig binds to B7-1 and B7-2 on antigen presenting cells and downregulates T cell activation by disrupting CD28-B7 costimulatory interaction. Abatacept blocks the interaction between CD28 expressed on the surface of T cells and CD80/CD86 on the surface of antigen-presenting cells. The drug was approved for RA by the FDA US (Food and Drug Administration) in 2005. Abatacept was compared to placebo in a randomized, placebo controlled, phase II trial of patients with active SLE characterized by arthritis, serositis, or rash (Merrill, Burgos-Vargas et al. 2010). SLE patients were randomized at a ratio of 2:1 to receive abatacept (10 mg/kg of body weight) or placebo. Prednisone (30 mg/day or equivalent) was given for 1 month, and then the dosage was tapered. There was no difference in the percentage of patients who experienced the primary endpoint of SLE flare, as defined by BILAG, over the course of 52 weeks. However, the investigators discerned a difference in flare rates between the abatacept group (64%) and placebo group (83%). This difference was especially pronounced in the subgroup of patients with arthritis. The frequency of adverse events was comparable in the abatacept and placebo groups (90.9% versus 91.5%), but serious adverse events were higher in the abatacept group (19.8 versus 6.8%). Most serious adverse events were single, disease-related events occurring during the first 6 months. Improvements in certain exploratory measures suggest that abatacept has some efficacy in patients with non-life-threatening manifestations of SLE.

5. Anticytokine monoclonal antibodies

In the course of SLE, a wide variety of cytokines is dysregulated, many of which are likely to influence autoimmunity and lupus tissue inflammation (La Cava. 2010; Robak, Kulczycka et al. 2007). They are not only involved in the immune dysregulation of SLE, but also in the local inflammatory response which ultimately leads to tissue injury. Proinflammatory cytokines such as tumor necrosis factor α (TNFα), iterleukin-6 (IL-6), IL-1 and interferon-γ (IFN-γ) may play an important role in propagating the inflammatory process responsible for tissue damage. IL-12, IL-15 and IL-18 are probably also involved in pathogenesis of SLE. The possibility of blocking the proinflammatory cascade by selective inactivation of cytokines can be a successful therapy for patients with SLE.

5.1 Anti-IL-6 monoclonal antibodies

Data from several studies suggests that IL-6 plays an important role in the B-cell hyperactivity and immunopathology of SLE (Klashman, Martin et al. 1991). One of the most important effects of IL-6 is to induce the maturation of B lymphocytes into plasma cells and augment the imunoglobulin secretion. IL-6 binds to the IL-6 receptors which belong to the type 1 cytokine receptor superfamily that consists of two subunits, namely the IL-6 R and the gp 130. This cytokine may have a direct influence in mediating tissue damage. Elevated levels of IL-6 were detected in the serum, urine and renal glomerulli of patients with active SLE and in murine models of SLE (Grondal, Gunnarsson et al. 2000).

Tocilizumab (ACTEMRA, MRA, Roche Pharmaceuticals) is a humanized anti-human IL-6R mAb considered as a therapeutic option for patients with SLE. It is an antibody which inhibits the interleukin-6 receptor. It binds to both soluble IL-6R and transmembrane IL-6R

and inhibit IL-6 binding to its receptors, leading to the blockade of IL-6 signaling through both receptors (Jones and Ding 2010). Tocilizumab suppresses the biological activity of IL-6 and is now being used in clinical trials for RA and SLE (ClinicalTrials.gov Identifier: NCT00046774). An intraperitoneal administration of an anti-IL-6 mAb decreased the production of anti-ds DNA antibodiess in murine model of SLE and prevented the development of severe kidney disease. These results suggest that treatment with anti-IL-6 mAb has a beneficial effect on autoimmunity in murine SLE and that autoreactive B cells may be the primary target for anti-IL-6 antibody treatment (Liang, Gardner et al. 2006).
Tocilizumab is an effective agent in all the stages of RA (Jones, Sebba et al. 2010). Tocilizumab is the first agent that has been shown to be superior to methotrexate (MTX) as monotherapy for the signs and symptoms of this disease. It is also an active drug in SLE patients. Tocilizumab when used in mild to moderate lupus patient has demonstrated preliminary success and good tolerability in an open-label phase I dosage-escalation study (Illei, Shirota et al. 2010). In this trial 16 patients with mild-to-moderate disease activity were assigned to receive 1 of 3 doses of tocilizumab given intravenously every other week for total of 7 infusions: 2 mg/kg in 4 patients, 4 mg/kg in 6 patients, or 8 mg/kg in 6 patients. Patients were then monitored for an additional 8 weeks. The median decrease in anti-dsDNA antibody levels at week 14 was −9 IU/ml (P = 0.03). There was improvement in overall disease activity over the course of treatment. Mean SLAM scores decreased from 7.1 at baseline to 5.0 at week 14 (P = 0.002), and mean mSELENA–SLEDAI scores decreased from 9.5 to 5.5 (P = 0.001). In addition, there was no SLE flare during the treatment period. The infusions were well tolerated, without any clinically significant infusion reactions. However, the treatment induced dosage-related decreases in the absolute neutrophil count, with a median decrease of 38% in the 4 mg/kg dosage group and 56% in the 8 mg/kg dosage group. Infections were observed in 11 patients between the start of study treatment and the end of the follow up period. This study provides the first evidence that treatment with tocilizumab has an acceptable safety profile and suggests a possible immunologic and clinical benefit in SLE.

5.2 Anti-IL 10 monoclonal antibody

Interleukin-10 (IL-10) is a cytokine produced mainly by monocytes and lymphocytes. It impedes the activation of antigen presenting cells, down-regulates the expression of co-stimulatory molecules and blunts T cell activation and TNF-α secretion. IL-10 boosts B cell proliferation and immunoglobulin class switching resulting in enhanced antibody secretion with the capacity to enter extravascular compartments and promote inflammation in SLE (Yap & Lai 2010). The levels of IL-10 increase in the serum of patients with active SLE and correlates with disease activity. Alteration in IL-10 regulation may result in accelerated T-cell apoptosis and aberrant T-cell dependent B-cell function. In animal models of lupus nephritis, anti-IL 10 blockade offered some benefits in limiting renal damage (Ravirajan, Wang et al. 2004). The beneficial effect of a combined therapy using both anti-IL-10 and anti-C5 mAb to prevent or reduce the effect of the humoral immune response in lupus disease was also suggested. Preliminary data has shown that anti-IL-10 monoclonal antibody improved cutaneous lesions, joint symptoms, and SLEDAI in lupus patients (Llorente, Richaud-Patin et al. 2000). The anti-IL-10 monoclonal antibody was administered to six patients with steroid resistant SLE in an open label pilot study. Treatment consisted of an 20 mg/day intravenous administration of an anti-IL-10 murine mAb (B-N10) for 21 consecutive days, with a follow-up period of 6 months. Therapy was well tolerated and marked improvement in skin lesions and joint symptoms was observed in all patients over the next 6 months. Furthermore, three times lower doses of

prednisone were used. The study indicates that the use of IL-10 antagonists may be beneficial in the management of refractory SLE.

6. Anti-CD40 and anti-CD40L monoclonal antibodies

CD40, a member of the tumor necrosis factor receptor super family, is highly expressed in normal B-cells and a variety of B-cell malignancies. CD40 ligand, also called CD154 or gp39, is a protein expressed on activated CD4+ T cells as well as on platelets, mast cells, macrophages, basophils, NK cells and B lymphocytes. An increased expression of CD40L has been found in the peripheral lymphocytes of patients with active SLE (Devi, Van Noordin et al. 1998). Moreover, serum levels of CD154 (CD40L) are higher in lupus patients than in normal persons (van Kooten & Banchereau 2000). The high expression of CD154 on T and B cells may increase production of potentially harmful auto-antibodies. The results of preclinical studies indicate that lupus-prone mice treated with anti-CD40L Abs had diminished inflammation, reduced anti-DNA autoantibody production and prolonged survival. Prolonged administration was particularly helpful in preventing fibrosis in severely nephritic mice (Kalled, Cutler et al. 2001). These results prompted the testing of anti-CD40L mAbs in human SLE.

6.1 Anti-CD40 monoclonal antibodies

Two mAbs directed against CD40 have been developed and investigated in preclinical studies and clinical trials, lucatumumab (HCD122) and dacetuzumab (SGN-40) (Kelley, Gelzleichter et al. 2006).

6.1.1 Lucatumumab

Lucatumumab ((HCD122, CHIR-0.12.12; Novartis Pharmaceuticals) is a fully human anti-CD40 mAb directed against the B-cell surface antigen CD40. It blocks CD40/CD40L interactions *in vitro* and inhibits CD40L-induced proliferation of human peripheral blood lymphocytes without disturbing baseline lymphocyte proliferation. Lucatumumab triggers cell lysis via ADCC in cells overexpressing CD40 (Luqman, Klabunde et al. 2008).

6.1.2 Dacetuzumab

Dacetuzumab (Seattle Genetics, Inc), is another humanized anti-CD40 IgG1 mAb, which induces ADCC and apoptosis of normal and malignant B-cells (Kelley, Gelzleichter et al. 2006). Dacetuzumab is able to initiate multiple signalling cascades upon ligation of CD40 on NHL cell lines. Dacetuzumab-mediated cytotoxicity is associated with up-regulation of cytotoxic ligands of the tumor necrosis factor (TNF) family including Fas/FasL, TNF-related apoptosis-inducing ligand, and TNFalpha.

6.2 Anti-CD40L monoclonal antibodies

6.2.1 IDEC-131

IDEC-131/E6040 (Idec Pharmaceuticals Corp. San Diego) is a humanized mAb against human CD154, comprising human γ1 heavy chains and human κ light chains with complementarity-determining regions of murine mAb clone 24-31. In Phase I clinical trial, IDEC-131 was administered in a single intravenous infusion at doses of 0.05-15.0 mg/kg in patients with SLE. Patients were followed for 3 months to evaluate toxicity and

pharmacokinetics (Davis, Totoritis et al. 2001). All patients experienced at least one adverse event. However, no infusion related cytokine-release syndrome was observed and all patients completed treatment. In a phase II, double blind, placebo-controlled, multiple-center, multiple-dose study, 85 patients with mild-to-moderately active SLE were randomized to receive 6 infusions of IDEC-131, ranging from 2.5 mg/kg to 10.0 mg/kg, or placebo over 16 weeks (Kalunian, Davis et al. 2002). At week 20, the mean change from baseline total SLEDAI scores indicated improvement in disease activity within each treatment group. In addition, the median global BILAG scores at week 20 indicated a reduction in SLE activity. However, results did not differ among the IDEC-131 treatment and placebo groups, and no dose-response relationship was noted at week 20. Moreover, the changes in levels of anti-dsDNA antibody and serum complement were not statistically significant in any group or between treatment groups and placebo. In addition, the changes in levels of anti-dsDNA antibody and serum complement were not different between treatment groups and placebo. The adverse events were also similar between the IDEC-131 and placebo groups.

6.2.2 BG9588

BG9588 (Biogen, Inc., Cambridge, MA) is a recombinant humanized anti-human CD40L monoclonal antibody that specifically binds to the CD40 ligand expressed on the surface of activated T lymphocytes. It blocks the CD40L/CD40 interaction between T and B cells that is required for the initiation for certain antibody responses. A short course of BG9588 treatment in patients with proliferative lupus nephritis reduced anti-dsDNA antibodies, increased C3 concentrations, and decreased hematuria (Boumpas, Furie et al. 2003). These results indicate that the drug has immunomodulatory action. Additional studies will be needed to evaluate its long-term effects.

7. Anticomplement antibody

Patients with SLE have widespread activation and deposition of the complement fragment in affected tissues. In murine models of SLE, the administration of the anti-C5 monoclonal antibody delayed the onset of proteinuria and prolonged survival. Moreover, pharmacological blockade of C5 receptor with a specific receptor antagonist reduces disease manifestation in experimental lupus nephritis (Cordeiro & Isenberg 2008). Furthermore, in mice with renal disease induced by a human anti-dsDNA antibody, RH-14 anti-C5 monoclonal antibody significantly reduced proteinuria.

Eculizumab (Soliris; Alexion Pharmaceuticals, Inc., Cheshire, CT) is a recombinant humanized monoclonal antibody that works by binding to complement protein C5, inhibiting its enzymatic cleavage, blocking formation of the terminal complement complex, and thus preventing red cell lysis (Parker , Kar et al. 2007). It has a molecular weight of 148 kD. Eculizumab is approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) (Hillmen, Young et al. 2006). This antibody is potentially useful for treating patients with lupus nephritis. In this disease, the terminal components of the complement C5b-C9 play an important role in mediating the inflammation and the damage of podocytes and glomerular basement membrane (Robak & Robak 2009). Eculizumab has been recently developed and investigated in a phase I single dose study in SLE.

MoAb	**Target**	**Antibody characteristics**
Rituximab	CD20	Type I, 1st generation $IgG_{1-\kappa}$, mAb, containing murine light– and heavy–chain variable–region sequences and human constant region sequences
Ocrelizumab	CD20	Type I, 2nd generation, humanized fusion IgG_1, binding to different CD20 epitope than rituximab, enhanced ADCC, reduced CDC, enhanced affinity for FcγRIIIa RIIIa
Veltuzumab (IMMU-106, hA20)	CD20	Type I, 2nd generation, humanized IgG_1, binding to different CD20 epitope than rituximab, enhanced ADCC, reduced CDC, enhanced affinity for FcγRIIIa RIIIa
Ofatumumab (HuMax-CD20, (Arzerra)	CD20	Type I, 2nd generation, Human IgG_1, binding to different CD20 epitope, more effective at CDC than rituximab
GA-101 (RO5072759)	CD20	Type II, 3rdgeneration, humanized IgG_1, superior ADCC than rituximab and superior direct cell-killing ability
AME-133v (LY2469298)	CD20	Type I, 3rd generation, humanized fusion IgG_1, enhanced affinity for FcγRIIIa, superior ADCC
PRO131921	CD20	Type I, 3rd generation, humanized fusion IgG1, improved binding to FcγRIIIa, better ADCC, superior anti-tumor efficacy
TRU-015	CD20	SMIP derived humanized fusion protein, ADCC and apoptosis induction
Epratuzumab (hLL2)	CD22	Humanized $IgG_{1-\kappa}$, , 90% to 95% of human origin , acting as an immunomodulatory agent, stimulating the CD22 molecule
Belimumab	BLyS	Fully human IgG_1 mAb that specifically binds and inhibits the biological activity of BLyS
Abatacept	B7-1 and B7-2	Recombinant fully humanized fusion protein, composed of the Extracellular domain of human CTLA-4 and a modified Fc part of IgG_1
Tocilizumab (ACTEMRA, MRA)	IL-6R	Recombinant, humanised monoclonal IgG_1 antihuman interleukin 6-receptor antibody
IDEC-131	CD40L	IDEC-131/E6040, humanized mAb against human CD154, comprising human γ_1 heavy chains and human κ light chains with complementarity-determining regions of murine mAb clone 24-31
BG9588	CD40L	Recombinant humanized anti-human CD40L mAb consists of the complementarity-determining regions of the murine monoclonal antibody 5c8 (anti-human CD40L antibody) with human variable-region framework residues and IgG_1 constant region

MoAb	Target	Antibody characteristics
Lucatumumab (HCD122, CHIR-0.12.12)	CD40	Human IgG_1 mAb that blocks CD40/CD40L interactions and inducesADCC
Dacetuzumab (SGN-40)	CD40	Humanized anti-CD40 IgG_1 mAb, which induces ADCC and apoptosis of B-cells
Eculizumab	Comple mentpro-tein C5	Recombinant humanized mAb binding to complement protein C5, inhibiting its enzymatic cleavage, blocking formation of the terminal complement complex

ADCC=antibody-dependent cellular cytotoxicity; BLyS=B-lymphocyte Stimulator;
CDC=complement-dependent cytotoxicity; mAb= monoclonal antibody;
SMIP=small modular immunopharmaceutical

Table 1. Monoclonal antibodies potentially useful in systemic lupus erythematosus

8. Conclusions

In recent years, clinical studies have been undertaken with selected mAbs in the treatment of SLE. The most frequently used mAb is rituximab, which is directed against CD20, a membrane protein expressed on B lymphocytes. Rituximab is effective in depleting B cells from peripheral blood, lymph nodes and bone marrow. Recent clinical studies confirm the high activity of rituximab in SLE patients, especially with lupus nephritis and neuropsychiatric involvement. Rituximab was generally well tolerated. However, occasionaly serious infections were reported. Over the last few years new generations of anti-CD20 mAbs have been developed for potential benefits over rituximab. They were engineered to have augmented antitumor activity by increasing CDC or ADCC activity and increased Fc binding affinity for the low-affinity variants of the FcγRIIIa receptor (CD16) on immune effector cells. This mAbs are are highly cytotoxic against B-cell lymphoid cells and are now being evaluated in clinical trials.

More recently, several newer mAbs have been developed and are being evaluated in phase I/II clinical trials. These include anti-cytokine therapies anti-CD40L mAbs, anti-CD-22 mAb, anti-BLys mAbs and anti- C5 mAbs. Belimumab is a fully human monoclonal antibody that binds to BLyS and inhibits its biological activity. Significantly positive results in both phase 3 studies have raised hopes that belimumab may be the long-awaited new effective therapy for SLE. Proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin- 6 (IL-6) play an important role in propagating the inflammatory process responsible for tissue damage. Blocking of these cytokines by mAbs can be also a successful therapy for patients with SLE. Finally, mAb eculizumab that specifically inhibits terminal complement activation has been recently developed and investigated in a phase I single dose study in SLE. These potentially useful agents should be further evaluated in well designed controlled trials.

9. Acknowledgements

This work was supported in part by the grants from the Medical University of Lodz (No 503-1093-1 and No No 503-1019-1). The authors have no conflicts of interest that are directly relevant to the content of this chapter.

10. References

Baker, K.P.; Edwards, B.M.; Main, S.H. et al. (2003) Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. *Arthritis Rheum.,* Vol.48. No 11, pp. 3253-3265, ISSN 1044-2626

Bologna, L.; Gotti, E.; Manganini, M. et al. (2011). Mechanism of Action of Type II, Glycoengineered, Anti- CD20 Monoclonal Antibody GA101 in B-Chronic Lymphocytic Leukemia Whole Blood Assays in Comparison with Rituximab and Alemtuzumab. *J Immunol.,* Vol. 186, No. 6, pp. 3762-3769, ISSN 0022-1767

Boumpas, D.T.; Furie, R.; Manzi, S. et al. (2003). BG9588 Lupus Nephritis Trial Group. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. *Arthritis Rheum.*, Vol. 48, No 3, pp. 719–727, ISSN 1044-2626

Burge, D.J.; Bookbinder, S.A.; Kivitz, A.J. et al. (2008). Pharmacokinetic and pharmacodynamic properties of TRU-015, a CD20-directed small modular immunopharmaceutical protein therapeutic, in patients with rheumatoid arthritis: a phase I, open-label, dose-escalation clinical study. *Clin Ther*, Vol. 30, No 10, pp. 1806-1816, ISSN 0149-2918

Cambridge, G.; Isenberg, D.A.; Edwards, J.C. et al. B cell depletion therapy in systemic lupus erythematosus: relationships among serum B lymphocyte stimulator levels, autoantibody profile and clinical response. *Ann Rheum Dis,*. Vol. 67, No. 7, pp. 1011-1016, ISSN 0003-4967

Cordeiro, A.C. & Isenberg, D.A. (2008). Novel therapies in lupus - focus on nephritis. *Acta Reumatol Port.,* Vol. 33, No. 2, pp. 157-169, ISSN 0303-464X

Czuczman, M.S. & Gregory SA. (2010). The future of CD20 monoclonal antibody therapy in B-cell malignancies. *Leuk Lymphoma.*, Vol. 51, No. 6, pp. 983-994, ISSN 1042-8194

Daridon, C.; Blassfeld, D. Reiter, K. et al. (2010). Epratuzumab targeting of CD22 affects adhesion molecule expression and migration of B-cells in systemic lupus erythematosus. *Arthritis Res Ther.*, Vol. 12, No. 6, pp. R204, ISSN 1478-6362

Davis, J.C. Jr.; Totoritis, MC.; Rosenberg, J. et al. (2001). Phase I clinical trial of a monoclonal antibody against CD40-ligand (IDEC-131) in patients with systemic lupus erythematosus.*J Rheumatol*, Vol. 28, No. 1, pp. 95-101, ISSN 0315-162X

Devi, B.S.; Van Noordin, S.; Krausz, T. & Davies, K.A. (1998). Peripheral blood lymphocytes in SLE—hyperexpression of CD154 on T and B lymphocytes and increased number of double negative T cells. *J Autoimmun.,* Vol. 11, No 5, pp. 471–475, ISSN 0896-8411

Dörner, T.; Kaufmann, J.; Wegener, W.A. et al. (2006). Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus. *Arthritis Res Ther.*, Vol. 8, No. 3, pp. R74, ISSN 1478-6362

Ermann, J.; Bermas, B.L. (2007). The biology behind the new therapies for SLE. *Int. J. Clin. Pract.*, Vol. 61, No. 12, pp. 2113-2119, ISSN 1368-5031

Faria, R.M. & Isenberg, DA. (2010). Three different B-cell depletion (anti-CD20 monoclonal antibodies) treatments for severe resistant systemic lupus erythematosus. *Lupus.*, Vol. 19, No. 10, pp. 1256-1257, ISSN 0961-2033

Furie, R.; Stohl, W.; Ginzler, E.M.; Becker, M.; Mishra, N.; Chatham, W.W, Merrill, J.T.; Weinstein, A.; McCune, W.J.; Zhong, J.; Cai, W.; Freimuth, W. (2008). Biologic activity and safety of belimumab, a neutralizing anti-B-lymphocyte stimulator (BLyS) monoclonal antibody: a phase I trial in patients with systemic lupus erythematosus. Study Group B. *Arthritis Res Ther*., Vol 110, No 5, R109, ISSN 1478-6362

Genovese, M.C.; Kaine, J.L.; Lowenstein, M.B. et al. (2008). Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I/II randomized, blinded, placebo-controlled, dose-ranging study. *Arthritis Rheum*, Vol. 58, No 9, pp. 2652-2661, ISSN 1044-2626

Goldenberg, D.M.; Rossi, E.A., Stein, R. et al. (2009). Properties and structure-function relationships of veltuzumab (hA20), a humanized anti-CD20 monoclonal antibody. *Blood*, Vol. 113, No 5, pp. 1062-1070, ISSN 0006-4971

Grondal, G.; Gunnarsson, I.; Ronnelid, J. et al. (2000). Cytokine production, serum levels and disease activity in systemic lupus erythematosus. *Clin Exp Rheumatol,* Vol. 18, No 5, pp. 565–570, ISSN 0392-856X

Hayden-Ledbetter, M.S.; Cerveny, C.G.; Espling, E. et al. (2009). CD20-directed small modular immunopharmaceutical, TRU-015, depletes normal and malignant B cells. *Clin Cancer Res,* Vol. 15, No 8, pp. 2739-2746 , ISSN 1557-3265

Hauptrock, B.& Hess, G. (2009). Rituximab in the treatment of non-Hodgkin's lymphoma. *Biologics,* Vol. 2, No. 4, pp.619-633 , ISSN 1177-5491

Hillmen, P, Young NS, Schubert J, et al. (2006). The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med.*, Vol. 355, No 12, pp. 1233-1243, ISSN 0028-4793

Illei, G.G; Shirota, Y.; Yarboro, C.H. et al. (2010). Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. *Arthritis Rheum.* Vol. 62, No. 2, pp. 542-552, ISSN 1044-2626

Jones, G. & Ding, C. (2010). Tocilizumab: a review of its safety and efficacy in rheumatoid arthritis. *Clin Med Insights Arthritis Musculoskelet Disord*., Vol. 19, No. 3, pp. 81-89, ISSN 1179-5441

Jones, G.; Sebba, A.; Gu, J. et al. (2010). Comparison of TCZ monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. *Ann Rheum Dis.* Vol. 69, No 1, pp. 88–96, ISSN 0003-4967

Kalled, S.L.; Cutler, A.H.; Ferrant, J.L. (2001). Long-term anti-CD154 dosing in nephritic mice is required to maintain survival and inhibit mediators of renal fibrosis. *Lupus,* Vol. 10, No 1, pp. 9–22, ISSN 0961-2033

Kalunian, K.C.; Davis, J.C. Jr.; Merrill, J.T. et al. (2002). IDEC-131 Lupus Study Group. Treatment of systemic lupus erythematosus by inhibition of T cell costimulation with anti-CD154: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.,* Vol. 46, No 12, pp. 3251–3258, ISSN 1044-2626

Kausar, F.; Mustafa, K.; Sweis, G. et al. (2009). Ocrelizumab: a step forward in the evolution of B-cell therapy. *Expert Opin Biol Ther,* Vol. 9, No pp. 889-895, ISSN 1471-2598

Kelley, S.K.; Gelzleichter, T.; Xie, D. et al (2006). Preclinical pharmacokinetics, pharmacodynamics, and activity of a humanized anti-CD40 antibody (SGN-40) in rodents and non-human primates. *Br J Pharmacol* Vol. 148, No 8, pp. 1116-1123, ISSN 1476-5381

King, J.K. & Hahn, B.H. (2007). Systemic lupus erythematosus: modern strategies for management: a moving target. *Best Pract Res Clin Rheumatol,*. Vol. 21, No. 6, pp. 971-987, ISSN 1521-6942

Klashman, D.J.; Martin, R.A.; Martinez-Maza, O. & Stevens R.H. (1991). In vitro regulation of B cell differentiation by interleukin-6 and soluble CD23 in systemic lupus erythematosus B cell subpopulations and antigen-induced normal B cells. *Arthritis Rheum*., Vol. 34, No. 3, pp. 276–286, ISSN 1044-2626

La Cava, A. (2010). Anticytokine therapies in systemic lupus erythematosus. *Immunotherapy,*. Vol. 2, No. 4, pp. 575-582.

La Cava, A. (2010). Targeting B cells with biologics in systemic lupus erythematosus. Expert Opinion *on Biological Therapy*, Vol. 10, No. 11, pp. 1555-1561, ISSN 1471-2598

Liang, B.; Gardner, D.B.; Griswold, D.E. et al. (2006). Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus. *Immunology,* Vol. 119, No 3, pp. 296–305, ISSN 0022-1767

Lim, S.H.; Beers, S.A.; French R.R. et al. (2010). Anti-CD20 monoclonal antibodies: historical and future perspectives. *Haematologica.,* Vol. 95, No 1, pp. 135-43, ISSN 0390-6078

Leandro, M.J.; Cambridge, G.; Edwards, J.C. et al. (2005). B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. *Rheumatology*, Vol. 44, No. 12, pp. 1542-1545, ISSN 0315-162X

Leonard, J.P. & Goldenberg, D.M. (2007). Preclinical and clinical evaluation of epratuzumab (anti-CD22 IgG) in B-cell malignancies. *Oncogene*, Vol. 26, No. 25, pp. 3704-13, ISSN 0950-9232

Llorente, L.; Richaud-Patin, Y.; Garcia-Padilla, C. et al. (2000). Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic Lupus erythematosus. *Arthritis Rheum*. Vol. 43, No. 8, pp. 1790 – 1800, ISSN 1044-2626

Lu, T.Y.; Ng, K.P.; Cambridge, G. et al. (2009). A retrospective seven-year analysis of the use of B cell depletion therapy in systemic lupus erythematosus at University College London Hospital: the first fifty patients. *Arthritis Rheum*, Vol. 61, No.4, pp. 482-487, ISSN 1044-2626

Luqman, M.; Klabunde, S. Lin, K. et al (2008).The antileukemia activity of a human anti-CD40 antagonist antibody, HCD122, on human chronic lymphocytic leukemia cells. *Blood* , Vol. 112, No 3, pp. 711-720, ISSN 0006-4971

Merrill, J.T.; Burgos-Vargas, R., Westhovens, R. et al. (2010). The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. Vol.62, No.10, pp. 3077-3087, ISSN 1044-2626

Merrill, J.T.; Neuwelt, C.M.; Wallace, D.J. et al. (2010). Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum.*, Vol. 62, No. 1, pp. 222-233, ISSN 1044-2626

Molloy, E.S.& Calabrese, LH. (2008). Progressive multifocal leukoencephalopathy: a national estimate of frequency in systemic lupus erythematosus and other rheumatic diseases. *Arthritis Rheum.*, Vol. 60, No. 12, pp. 3761-5, ISSN 1044-2626

Morschhauser, F.; Leonard, J.P.; Fayad, L. et al. (2009). Humanized anti-CD20 antibody, veltuzumab, in refractory/recurrent non-Hodgkin's lymphoma: phase I/II results. *J Clin Oncol.* Vol. 27, No. 20, pp. 3346-3353, ISSN 0732-183X

Navarra, S.V.; Guzmán, R.M.; Gallacher, A.E. et al. BLISS-52 Study Group. (2011). Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet.*, Vol. 377, No. 9767, pp. 721-731, ISSN 0140-6736

Ng, K.P.; Cambridge, G., Leandro, M.J. et al. (2007). B cell depletion therapy in systemic lupus erythematosus: long-term follow-up and predictors of response. *Ann Rheum Dis,*. Vol. 66, No. 9, pp. 1259-62, ISSN 0003-4967

Østergaard, M.; Baslund, B.; Rigby, W. et al. (2010). Ofatumumab, a human anti-CD20 monoclonal antibody, for treatment of rheumatoid arthritis with an inadequate response to one or more disease-modifying antirheumatic drugs: results of a randomized, double-blind, placebo-controlled, phase I/II study. *Arthritis Rheum.*, Vol. 62, No. 8, pp. 2227-2238, ISSN 1044-2626

Parker, C.J.; Kar, S. & Kirkpatrick, P. (2007). Eculizumab. *Nat. Rev. Drug Discov*. Vol. 6, No 7, pp. 515–625, ISSN 1474-1776

Pepper, R.; Griffith, M.; Kirwan, C. et al. (2009). Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids. *Nephrol Dial Transplant.*, Vol. 24, No. 12, pp. 3717-3723, ISSN 0931-0509

Ravirajan, C.T.; Wang, Y.; Matis, L.A. et al. (2004) Effect of neutralizing antibodies to IL-10 and C5 on the renal damage caused by a pathogenic human anti-ds DNA antibody. *Rheumatology.* Vol. 43, No 4, pp. 442–447. , ISSN 0315-162X

Robak, T. (2004). Monoclonal antibodies in the treatment of autoimmune cytopenias. *Eur J f Haematol.*, Vol. 72, No. 2, pp.79-88, ISSN 0902-4441

Robak, E.; Kulczycka, L.; Sysa-Jedrzejowska, A. et al. (2007). Circulating proangiogenic molecules PIGF, SDF-1 and sVCAM-1 in patients with systemic lupus erythematosus. *Eur Cytokine Netw.,* Vol. 18, No. 4, pp. 181-7, ISSN 1148-5493

Robak, T. (2008). Ofatumumab, a human monoclonal antibody for lymphoid malignancies and autoimmune disorders. *Curr Opin Mol Ther.,* Vol. 10, No. 3, pp. 294-309, ISSN 1355-6568

Robak, T. (2009). GA-101, a third-generation, humanized and glyco-engineered anti-CD20 mAb for the treatment of B-cell lymphoid malignancies. *Curr Opin Investig Drugs.*, Vol. 10, No. 6, pp. 588-596, ISSN 1472-4472

Robak, T.; Robak, P. & Smolewski P. (2009). TRU-016, a humanized anti-CD37 IgG fusion protein for the potential treatment of B-cell malignancies. *Curr Opin Investig Drugs*, Vol. 10, No pp. 1383-1390, ISSN 1472-4472

Robak, E. & Robak, T. (2009). Monoclonal antibodies in the treatment of systemic lupus erythematosus. *Curr Drug Targets,,* Vol. 10, No 1, pp. 26–37, ISSN 1389-4501

Robak, T & Robak, E. (2011). New anti-CD20 monoclonal antibodies for the treatment of B-cell lymphoid malignancies. *BioDrugs*, 2011 Vol. 25, No. 1, pp.13-25, ISSN 1173-8804

Rubbert-Roth, A. (2010). TRU-015, a fusion protein derived from an anti-CD20 antibody, for the treatment of rheumatoid arthritis. *Curr Opin Mol Ther.*, Vol. 12, No. 1, pp. 115-123, ISSN 1355-6568

Ruuls, S.R.; Lammerts van Bueren J.J.; van de Winkel J.G. et al. (2008). Novel human antibody therapeutics: the age of the Umabs. *Biotechnol J,* Vol. 3, No pp. 1157-1171, ISSN 0268-2575

Schröder, J.O. & Zeuner, R.A. (2009). Biologics as treatment for systemic lupus: great efforts, sobering results, new challenges. *Current Drug Discovery Technologies* , Vol.6, No. 4, pp. 252-255, ISSN 1570-1638

Sfikakis, P.P.; Boletis, J.N.; Lionaki, S. et al. (2005). Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the T cell costimulatory molecule CD40 ligand: an open-label trial. *Arthritis Rheum,.* Vol. 52, No. 2, pp. 501-513, ISSN 1044-2626

Smith, K.G.; Jones, R.B.; Burns, S.M. & Jayne, D.R. (2006). Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. *Arthritis Rheum.,* Vol. 54, No. 9, pp. 2970-82, ISSN 1044-2626

St Clair, E.W. (2009). Novel targeted therapies for autoimmunity. *Curr Opin Immunol.* Vol. 21, No. 6, pp.648-657, ISSN 0952-7915

Terrier, B.; Amoura, Z.; Ravaud, P. et al. Club Rhumatismes et Inflammation. (2010). Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. *Arthritis Rheum.,* Vol. 62, No. 8, pp. 2458-66 , ISSN 1044-2626

Tokunaga, M.; Saito, K.; Kawabata, D. et al. (2007). Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. *Ann Rheum Dis.,* Vol. 66, No. 4, pp. 470-5, ISSN 0003- 4967

Toubi, E.; Kessel, A.; Rosner, I. et al. (2006). The reduction of serum B-lymphocyte activating factor levels following quinacrine add-on therapy in systemic lupus erythematosus. *Scand J Immunol.,* Vol. 63, No. 4, pp. 299-303, ISSN 0301-6323

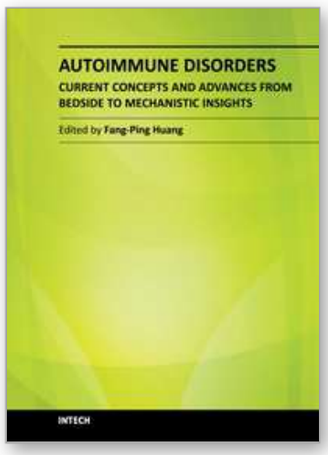
van Kooten, C.; Banchereau, J. (2000). CD40-CD40 ligand. *J Leukoc Biol* ,Vol. 6, pp. 2-17, ISSN 0741-5400

Wallace, D.J.; Stohl, W.; Furie, R.A. et al. (2009). A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum.,* Vol. 61, No 9, pp. 1168–1178, ISSN 1044-2626

Wiglesworth, A.K.; Ennis, K.M. & Kockler, D.R. (2010). Belimumab: a BLyS-specific inhibitor for systemic lupus erythematosus. *Ann Pharmacother.*, Vol. 44, No.12, pp. 1955-61, ISSN 1060-0280

Willems, M.; Haddad, E.; Niaudet, P.; Koné-Paut, I. et al. French Pediatric-Onset SLE Study Group. (2006). Rituximab therapy for childhood-onset systemic lupus erythematosus. *J Pediatr.*, Vol. 148, No. 5, pp. 623-627, ISSN 0271-6798

Yap, DY.; Lai, KN. (2010). Cytokines and their roles in the pathogenesis of systemic lupus erythematosus: from basics to recent advances. *J Biomed Biotechnol,* 2010:365083. Epub 2010 May 6. ISSN 1110-7243.



Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights

Edited by Dr. Fang-Ping Huang

ISBN 978-953-307-653-9
Hard cover, 614 pages
Publisher InTech
Published online 14, November, 2011
Published in print edition November, 2011

Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ewa Robak and Tadeusz Robak (2011). The Emerging Role of Monoclonal Antibodies in the Treatmentof Systemic Lupus Erythematosus, Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights, Dr. Fang-Ping Huang (Ed.), ISBN: 978-953-307-653-9, InTech, Available from: http://www.intechopen.com/books/autoimmune-disorders-current-concepts-and-advances-from-bedside-to-mechanistic-insights/the-emerging-role-of-monoclonal-antibodies-in-the-treatmentof-systemic-lupus-erythematosus

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen