B Cell Targeting: Current and Future Agents

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Learning Objectives

• Review the roles of B cells in autoimmune disease.
• Biologics with diverse MOA that target B cells.
• Discuss hypotheses regarding the efficacy of B cell targeted therapy in the treatment of autoimmune disease.
• Consider new therapeutic approaches to target B cell survival factors and CD20 on B lineage cells.
• Discuss emerging data on ACPA antibodies and pathogenesis
Autoimmunity and Pathogenetic B-cell mechanisms

Lymphoid organogenesis
- Multiple sclerosis
- Sjögren’s syndrome
- RA

Antigen presentation and costimulation
- Multiple sclerosis
- SLE
- RA

Auto-antibodies
- Graves’ disease
- Myasthenia gravis
- Pemphigus vulgaris
- SLE
- RA

Immune complexes
- SLE
- RA

Adapted from Martin Ann Rev Immunol 2006;24:467-96.

Different Approaches to Target B Cells:
Differential impact on B Cell Development

Stem Cell

Pro/Pre B Cell

Immature B cell

Transitional B cell

Mature B cell

Antibody-producing Plasma cells

Rituximab (anti-CD20)
- Binds and eliminates CD20-positive cells

Belimumab (antisoluble BAFF/BLyS)
- Acts later in B-cell development

Atacicept (TACI-Ig)
- Neutralizes both BLyS/BAFF and APRIL
- Acts later in B-cell development
- Potently inhibits Ig-secreting cells

Courtesy of G. Silverman
Targeting of CD20: New MAbs in Development

**CD20**
- 297 amino acid phosphoprotein with four transmembrane domains.
- plays a critical role in B-cell development.
- functions through Src family tyrosine kinases, such as Lyn, Fyn, and Lck
  - result in phosphorylation cascade of intracellular proteins.
- remains on the membrane of B cells without dissociation or internalization upon antibody binding (reviewed in 1).


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**Rituximab (RTX)**
- first generation anti-CD20 mAb (1),
- can induce complement-dependent cytotoxicity (CDC),
- antibody-dependent cellular cytotoxicity (ADCC),
- can lead to apoptosis of B cells upon binding to CD20 and thereby directly inhibit cell growth [2].
- Recent studies implicate reactive oxygen species mediated through NADPH (2).
- FDA approved for B cell neoplasm, TNF IR RA, granulomatous polyangiitis

B cell subsets in the blood

- CD27+ memory B cells
- Plasmablasts

Clinical efficacy and the B-Cell Regeneration Pattern in RA After Rituximab Treatment

- CD27+ memory B cells
- Naive B cells

A: P < .001 vs baseline.
B: P < .05 vs baseline.
C: P < .05 vs mos 5-6 after the first treatment.
Potential implications of therapeutic reductions in memory B cells in autoimmune diseases

• Memory B cells have lowest thresholds for BCR triggering
• Antigen specific memory B cells are likely the most important APCs in the body
• Therapeutic benefits in RA may require removal of memory B cells and PC-like cells from RA synovium, the site of ectopic lymphoid tissue responsible for disease.
• Affected B cell subset pharmacodynamics vary greatly between different agents.
• All current biologic MOA have effects on B-cell activation, memory and function.

BLyS and APRIL play roles in ensuring survival of B cells

• Potentially expressed by multiple immune cells\(^1,2\)
  – neutrophils
  – monocytes
  – Dendritic cells
  – activated T cells
  – plasma cells
  – B cells
• Discovered in 1998, BLyS/BAFF (TNFSF13B) exists in membrane-bound and soluble forms\(^1\). Related A proliferation associated ligand (APRIL, TNFSF13) overlapping effects
• Three molecules bind together to form the trimeric soluble protein\(^1,3\)
  – soluble BLyS is considered to be the only active form of BLyS\(^3\)
• BLyS is important in ensuring that new B cells mature, survive and differentiate\(^1,3\)

BLyS (BAFF) levels elevated in SLE and RA


Approaches to block BLyS/APRIL

- Blisimod (A623) soluble and membrane bound BLyS
- Tabalumab (LY2127399) soluble and membrane BLyS

Tabalumab in RA with Methotrexate IR and Biologics naïve: Phase II Placebo-Controlled Trial

Tabalumab, fully human IgG4 monoclonal antibody, neutralizes soluble and membrane-bound BAFF.

Phase II suggested clinical efficacy, but no dose response incidence of adverse events was similar in all groups; no deaths occurred.

IgM levels decreased significantly in all tabalumab groups compared with the placebo group.

No significant decreases in serum IgG or IgA levels

Effects of anti-BlyS on blood B cell subsets
Belimumab phase II SLE trial

Decreases mature and plasma B cells but spares memory B cells and B cell progenitors

Belimumab FDA approved for SLE!
Effect of anti-BLyS Rx on SLE Activity: Combined responder Index (CRI) *Belimumab phase II trial*

Clinical benefits supported FDA approval in non renal SLE

**Petri et al, ACR 2009**

Tabalumab in RA with Methotrexate IR and Biologics naïve: Phase II Placebo-Controlled Trial

Same effects on B cell levels as Belimumab

• Blockade of BAFF (BLyS) reduces naïve B cells, and causes short term increases in blood CD27+ memory B cells

• Feb. 7, 2013 -- discontinuation of Phase 3 RA program for tabalumab, an anti-BAFF antibody, due to lack of efficacy. Decision was not based on safety concerns.

• Tabalumab Phase 3 program for SLE, ILLUMINATE, is ongoing and will continue as planned

• Clinical benefits of BAFF blockade in RA have been limited.

• Is the limited efficacy of BAFF blockade in RA due to effects on B cell subsets (i.e., no effect on memory B cells)?

Second generation anti-CD20

Ofatumamab approved for CLL
early trials in RA

Veltuzumab

Ocrelizumab early trials in RA and SLE – halted multiple sclerosis – ongoing trials

Third generation anti-CD20

GA101 (Obinutuzumab) NHL FL

PRO131921 Refractory NHL

Ocaratuzumab (AME-133v) FL early RA
Efficacy of anti-CD20 in RA

Best dosing regimen for induction? One dose loading or split doses?

Roadblock Hypothesis: Implications for Dosing regimens
Ocrelizimab – 2\textsuperscript{nd} generation anti-CD20

![Graph showing pharmacokinetic profile of Ocrelizimab](image)

*Figure 3. Pharmacokinetic profile over 24 weeks after one course of single-infusion (400 mg \times 1) and dual-infusion (200 mg \times 2) ocrelizumab.*

Ocrelizimab: Lessons on induction

Huffstutter et al

Split dose

RTX was originally developed for the treatment of NHL, a B cell malignancy

The rationale for the original FDA approved dosing regimen was at best empiric

Dosing regimens for induction or maintenance of responses in RA and other autoimmune diseases have not been adequately investigated

Figure 2. Proportion of patients achieving American College of Rheumatology 20/50/70 responses at week 24 in the intent-to-treat population. p-values shown only for primary efficacy comparison of OCR 400 mg × 1 versus placebo.


Int J Clin Rheumatol (2011) 6(6), 680–696

Dosing regimens for RTX

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- The rationale for the original FDA approved dosing regimen was at best empiric
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Ofatumumab (700 mg IV repeat in 2 wks) (with MTX and pred ≤10 mg/d)

MTX IR of > 6 months duration, 8 or more swollen and tender joints, elevated CRP or ESR


Current status of second generation anti-CD20 agents in RA

OCRE Phase III program in RA patients terminated
- due to serious infections in pts that received 2 × 500 mg OCRE in Asia–Pacific region (18.1 events/100 pt-years vs. 2.6 placebo), other parts of the world serious infections were comparable between OCRE and placebo patients.
- No PML after OCRE administration reported.
- Nearly all OCRE-associated infections in RA patients with exception of two pneumonia cases – resolved with appropriate therapy.

OCRE development in RA discontinued

Ofatumumab development program for RA is ongoing.

Both OCRE and Ofat in development for MS
Ocaratuzumab (OCAR), previously known as AME-133v

- Fc- and Fab-engineered, humanized, anti-CD20 monoclonal antibody
- 13-20 fold higher affinity for CD20
- 36 amino acid changes in H chain and 28 in L chain, vs. human IgG1
- 6-fold higher antibody-dependent cellular cytotoxicity (ADCC) vs. RTX.
- Low levels of complement-mediated cytotoxicity (CDC) may lower infusion reactions

In NHL, inheritance of low affinity FcγRIIIa variant is associated with worse responses to RTX, therefore higher affinity binding of anti-CD20 for FcγRIIIa was evaluated

O'Reilly et al. ACR 2012. Abs 835.

Ocaratuzumab depletes healthy B-cells at 2 log orders less than the dose of rituximab

O'Reilly et al. ACR 2012. Abs 835.
Complement dependent cytotoxicity (CDC)

Ocaratuzumab (AME-133v) demonstrates 3.5- to 8-fold higher ADCC than rituximab

Ocaratuzumab triggers ADCC at concentrations 2 log orders less than the dose of rituximab

Standard doses (1 gm x2) increases blood BAFF levels assoc. with B cell depletion (1). BAFF levels also increase after very low dose OCAR (2)
Third Generation Anti-CD20: Ocaratuzumab (OCAR)

B-cell killing mechanisms of selected anti-CD20 antibodies

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<th>Rituximab</th>
<th>Ofatumumab</th>
<th>Ocaratuzumab</th>
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B cell targeted therapy: An evolutionary view

Targeting of BCR and soluble Ig/Abs
- Microbial B cell toxins → anti-idiotypes

B cell membrane-associated targets and B cell survival factors
- RTX → 2nd/3rd generation anti-CD20
- BAFF/APRIL targeting

Beyond!
Key Findings with New Anti-CD20 Agents

- Anti-CD20 targeting, the prototypic B cell targeting MOA (i.e., RTX), remains a highly attractive approach for the treatment of many autoimmune diseases.

- Protein engineers can alter an antibody’s ligand binding affinity, as well as IgG constant region associated properties, which may provide new therapeutic opportunities.

- Preclinical studies and early phase trials highlight the novel properties of OCAR, and may provide a means for effective B cell targeting with very low antibody doses (relevant to development of SQ agents) and reduced CDC may reduce infusion reactions.

- Further trials are merited.

Antibody levels to CCP3 does not separate out RA subsets
Heterogeneity of ACPA profiles may help to identify RA pts with different risks for clinical outcomes

ELISA assays to citrullinated peptides for CCP3 and 5 natural self proteins

ACPA Repertoire spreading with disease progression

Gronwall, Scher and Greenberg (NYU Unpublished)
Cell and Cytokine Traffic Through Rheumatoid Joints

In RA, high TNF-α and IL-1 levels suppress CXCL12-mediated retention of B cells in bone marrow, resulting in increased trafficking.

Serum ACPA levels may be proportional to levels of circulating memory B cells.

Cardiovascular death 2-3 fold increased in RA, but only for ACPA positive not seronegative.

Is ACPA autoantibody production part of CV pathogenesis?

Retrospective study 152/3052 healthy males (no RA).
IgG anti-CCP2 found in 10.2% of patients with CV events, 3.8% of controls (OR 3.26 P<0.008), which remained significant after adjustment for other risk factors, including smoking and CRP.

Preclinical phase?

Summary

- B cell targeting has become a widely accepted clinical paradigm for the treatment of autoimmune diseases.
- Recent experience may suggest that BlyS/APRIL targeting may not be highly efficacious in most RA patients.
- Targeting of CD20 provides an attractive MOA to treat RA and perhaps other B cell driven autoimmune diseases.
- Efficacy may involve targeting of (disease-associated memory) B cells in pathogenesis without seriously harming overall immune defenses.
- Further studies on the direct roles of disease-associated memory B cells may provide new therapeutic opportunities.