

Systemic lupus erythematosus had a past-a past drenched with “blood”, “sweat” and “tears”. But what is its future-a gloomy future, or is there any silver lining?

Before any therapeutic plan to any disease first we will have to know who the culprit is.

- Therapeutic Targeting of B Cells

A central role for B cells in SLE pathogenesis has long been accepted although definitive evidence in support of such a conclusion is limited to mouse studies. Genetic depletion of B cells from lupus-prone MRI Lpr or N2M 2328 mice completely protects them from developing the disease.<sup>1</sup>

B cells in patients with SLE can be conceptually divided into three functional groups-

1. Autoreactive B cells – responsible for autoimmune disease
2. Protective B cells-that help to promote and effect immunity against foreign antigens.
3. Regulatory B cells ( $B_{reg}$ )-that help to keep immune responses, both pathological and protective, in check.

So an ideal therapeutic approach will be to kill only the autoreactive or “bad” B cells.

In principle, B cells can be targeted directly or indirectly; B cells itself are targeted directly by therapeutic agents or indirectly by targeting cytokines released by B cells.

- B cell depletion and inactivation

- CD20-targeted therapy

CD 20 is a surface marker specific for the B cell lineage.

Rituximab is a monoclonal antibody (mAb) and triggers B cell death via antibody-dependent cell mediated cytotoxicity (ADCC).<sup>2</sup> The initial open label experience with rituximab in SLE was encouraging.<sup>3</sup> But two double-blinded phase II/III randomised placebo-controlled trials (RCTs) with rituximab in SLE or lupus nephritis (n=257 and n=144 respectively) failed to meet their primary or secondary endpoints.<sup>4</sup>

Ocrelizumab, a second anti-CD20 mAb has also been tested in a double-blinded phase III RCT in lupus nephritis (n=381). Although there was a trend towards greater renal responses among

ocrelizumab treated patients than among placebo treated patients, the frequency of serious and opportunistic infections in the ocrelizumab group was sufficiently great, so the sponsor had to discontinue dosing.

- CD19-targeted therapy

CD19 is also a surface marker for B-lineage cells, being expressed from the pro-B cell stage until the plasma cell stage.

Two atucosylated anti-CVD19 mAbs, MEDI-551 and MDX-1342, have been developed that can deplete human B cells in vitro and monkey B cells and human CD19-expressing mouse B cells in vivo.<sup>5</sup>

- CD22-targeted therapy

Two phase III double-blinded RCTs in SLE with epratuzumab at cumulative dose are currently underway<sup>6</sup>, so important information regarding the efficacy and safety of CD22 targeted therapy should emerge in the near future.

- Fc $\delta$ RIID-targeted therapy

B cell function can be downregulated without depletion of B cells by Fc $\delta$ RIID-directed therapeutics.

- Generation of  $B_{reg}$  cells

$B_{reg}$  cells are IL-10 producing B cells that were initially identified by their ability to downregulate experimental autoimmune encephalomyelitis and intestinal inflammation in mice.<sup>7</sup>

CD40- directed stimulation of  $B_{reg}$  cells promotes their expansion, increases their production of IL-10 and enhances suppressor activity.

No clinical trials with anti-CD40 mAbs in SLE are currently underway. Some limited experience with anti-CD40 is being obtained in human inflammatory disorders, namely a phase II trial with an anti-CD40 mAb, ASKP 1240 in patients with moderate- to- severe plaque psoriasis<sup>8</sup> is going on. Favourable results from this trail might spur interest in testing anti-CD40 mAbs in human SLE.

- Therapeutic Targeting of T Cells

Rationale

Like B cells, an important role for T cells in

SLE pathogenesis has long been appreciated. A thymic BWF<sub>1</sub> mice (which lack functional T cells) do not develop lupus, and disease can be fully reconstituted following engraftment of a thymus.<sup>9</sup>

- T-cell tolerance

T cells can be conceptually divided into 3 functional groups-

1. Pathogenic T cells
2. Protective T cells
3. Regulatory T cells

In contrast to the great interest in B-cell depletion as a therapeutic approach, Pan-T-cell depletion or CD4+ T-cell depletion as a therapeutic approach has received little consideration.

Making the autoreactive T cells immunologically unresponsive to the relevant self antigens might represent a safer and hence more prudent approach.

- Blockade of T cell activation and differentiation

CD28 targeted therapy i.e., Abatacept showed efficacy in a mouse lupus model but results from clinical trials of abatacept in human SLE have been disappointing

- T-cell trafficking and Integrin-targeted therapy

Even if pathogenic T cells do succeed in becoming fully activated and differentiated they would remain incapable of triggering and effecting end organ damage if prevented from reaching the end organ. Substantial efficacy was achieved in patients with severe recalcitrant discoid lupus with off-label use of efalizumab, a mAb specific for  $\alpha$ L integrin that inhibits T cell migration into target tissues.

- Therapeutic Targeting of Cytokines:targeting Baff (Beta Cell Activating Factor)

Despite the success of the phase III trials with intravenous belimumab and its outstanding safety profile, belimumab remains far from being a panacea for SLE. Strikingly enough, patients with severe active nephritis or central nervous system disease were excluded from these phase III trials. So, ironically, we have no information yet regarding the efficacy or safety of belimumab in those patients who arguably have the greatest unmet therapeutic need.

Despite targeting B-cells and T-cells from different angles our success to conquer SLE is far from satisfactory. So, is there any other culprit?

- Dendritic Cells (DC)

Blood contains 2 DC subsets-

1. A CD11c (-) one
2. A CD11C (+) one

The CD11c (-) subset, called plasmacytoid DC (PDCs)

comes from an independent, possibly lymphoid related, differentiation pathway and secretes interferon- $\gamma$ .

The CD11c (+) subset follows a myeloid differentiation pathway-hence called myeloid DC (MDCs) -where monocytes serve as the reservoir of precursors.

SLE appears as a disease with major alteration in DC subset homeostasis-while one DC subset i.e., PDC is dramatically reduced in the blood (possibly due to accelerated migration into tissue) and the normally quiescent monocytes act as MDC.Thus unabated DC induction may drive the autoimmune response in SLE and this may be controlled by targeting IFN- $\alpha$ .

- IFN- $\alpha$  in the Pathogenesis of SLE

The release of IFN $\alpha$  by PDC induces monocytes to differentiate into DCs.These cells efficiently capture apoptotic cells and nucleosomes, present in large amounts in SLE blood.These antigen-loaded DC are further activated by IFN $\alpha$  and present self antigens to autoreactive T-cells and B-cells.Such a "ménage a trois" generates a high number of plasma cells producing antibodies, which form immune complexes that may sustain IFN $\gamma$  production.<sup>10</sup> Furthermore high IFN levels explain T and B-cell lymphopenia.

## CONCLUSION

Current treatment approaches in SLE are based on non-specific immunosuppression. Current disease models propose IFN $\gamma$  at the centre of the immunological abnormalities observed in SLE, and poses IFN $\gamma$  and IFN $\alpha$ -producing cells as novel targets for therapy in this disease. It is now necessary to develop clinically relevant agents that would block either IFN $\alpha$  production or its biological activity.One of the potential therapeutic targets could be BDCA-2, a novel plasmacytoid dendritic cell-specific type II C lectin, which blocks the induction of type I interferons by PDCs.<sup>11</sup> Our greatest hope is that blocking type I IFN will bring SLE patients the relief that blocking TNF is bringing to patients with rheumatoid arthritis.

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