



New Treatments for Lupus: an evolving landscape

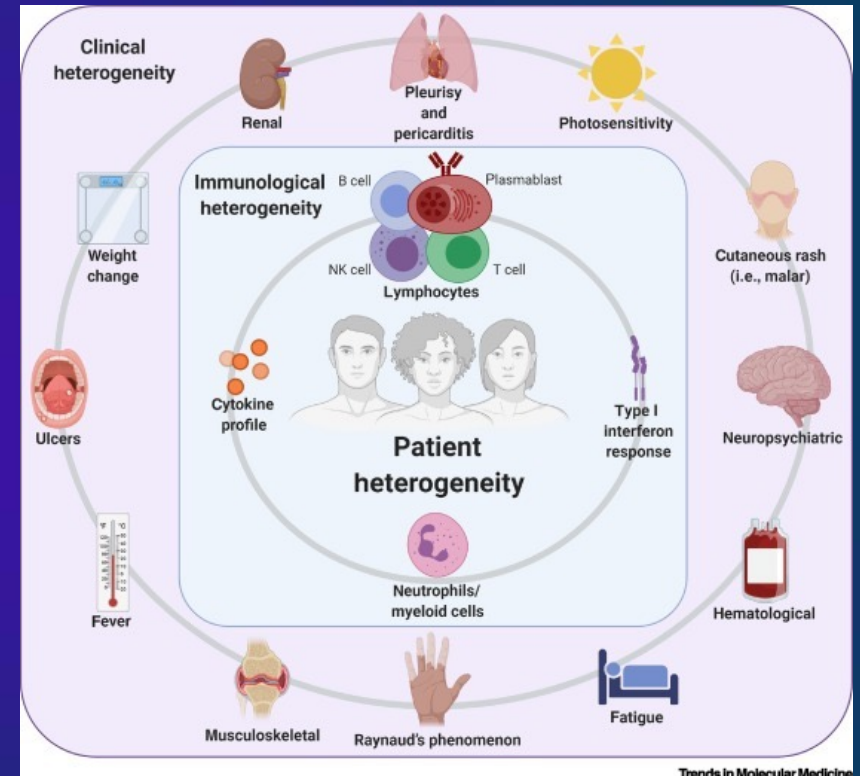
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Lupus Disease Activity

- ▶ Lupus is a very heterogenous, variable disease
- ▶ Variations occur in several ways
 - ▶ Some patients have mild disease with easily controlled flares
 - ▶ Some individuals may have lupus in just one or two organs (kidney limited disease)
 - ▶ Other have more severe disease involving several different organs such as the heart and kidney and blood
 - ▶ Lupus inflammation or disease activity can vary over time
 - ▶ Pediatric lupus vs adult onset
 - ▶ Some individuals may experience frequent flares, while others may have them very sparingly
- ▶ Variations in diseases are likely related to different immune pathways



Trends in Molecular Medicine

Trends in Molecular Medicine
Feb 2021

Goals of lupus treatment

- ▶ Limit flares and prevent organ damage!
- ▶ Limit steroid use over lifetime
- ▶ Improve quality of life
- ▶ Different definitions about achieving remission or low disease activity state:
 - ▶ Remission: No active lupus, stable on hydroxychloroquine and no steroids
 - ▶ Low level disease activity: very little signs of active lupus, stable on low dose prednisone (less than 7.5 mg daily, and on hydroxychloroquine)

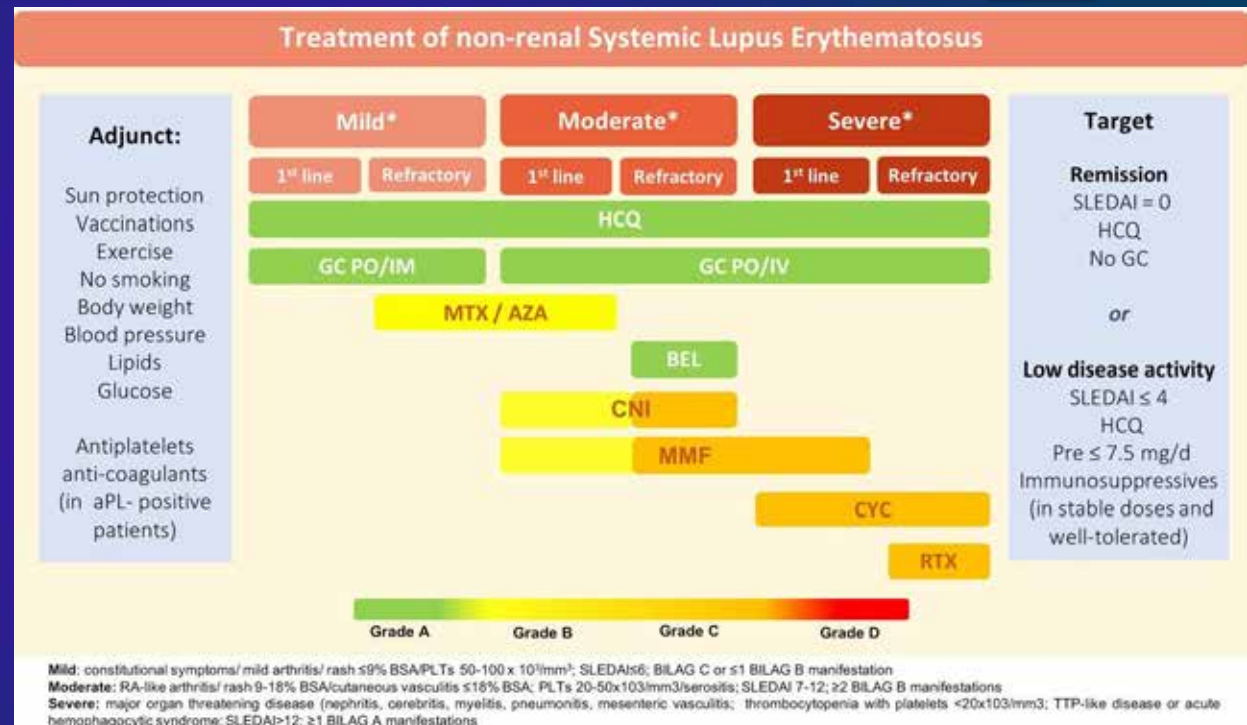
Current Drug Treatments

▶ FDA approved Drugs:

- ▶ Steroids (1950s)
- ▶ Low Dose Aspirin (1950s)
- ▶ Hydroxychloroquine (1956)
- ▶ Belimumab (2011)
- ▶ Belimumab for Kidney lupus (2020)
- ▶ Voclosporin (January 2021)
- ▶ Anifrolumab (August 2021)

▶ Other standard of care lupus drugs

- ▶ Cyclophosphamide
- ▶ Azathioprine
- ▶ Mycophenolate Mofetil
- ▶ Methotrexate
- ▶ Tacrolimus
- ▶ Cyclosporine
- ▶ Rituximab



EULAR 2019 Lupus treatment guidelines

Why do we need new therapies?

- ▶ Safer and more effective therapies with less side effects, Replace Steroids
- ▶ Refractory Severe Disease (such as severe kidney disease or multiorgan disease)
 - ▶ 20% of patients with lupus nephritis progress to end stage kidney disease requiring dialysis
- ▶ Replace immune-suppressives and chemotherapy with more targeted treatment
- ▶ Prevent flares
- ▶ Improve quality of life
- ▶ Other Unmet needs in Lupus/ The “other” symptoms of lupus
 - ▶ Fatigue
 - ▶ Concentration difficulties
 - ▶ Depression
 - ▶ Pain
- ▶ Decrease Cardiovascular risk

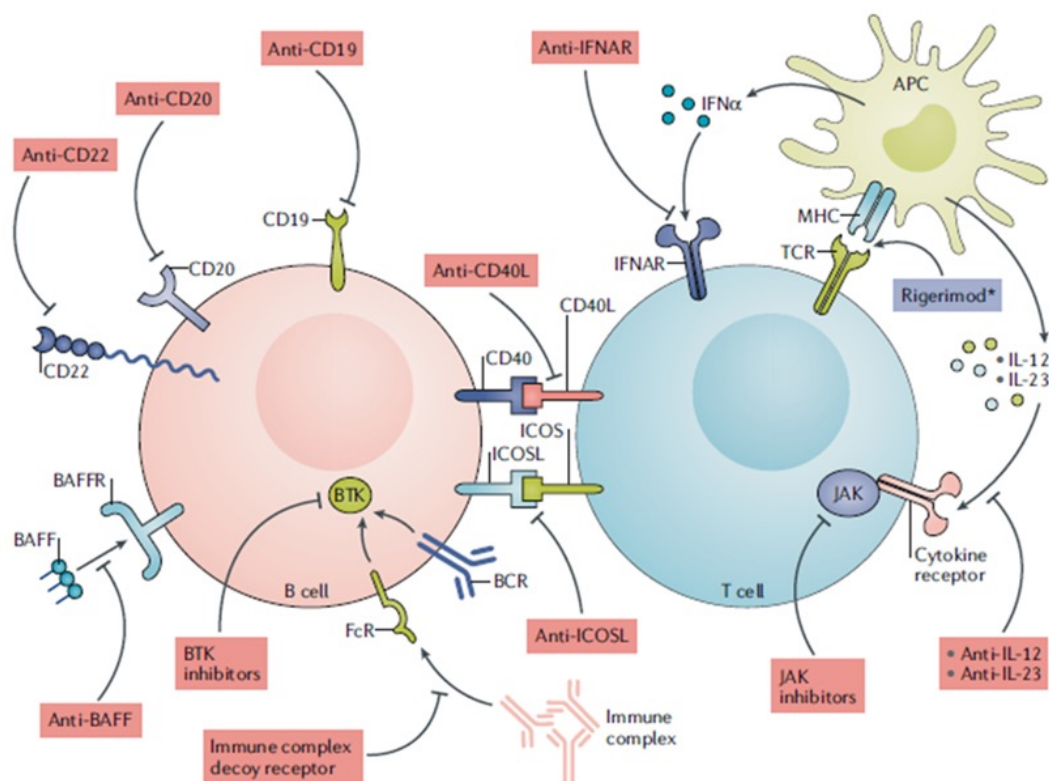
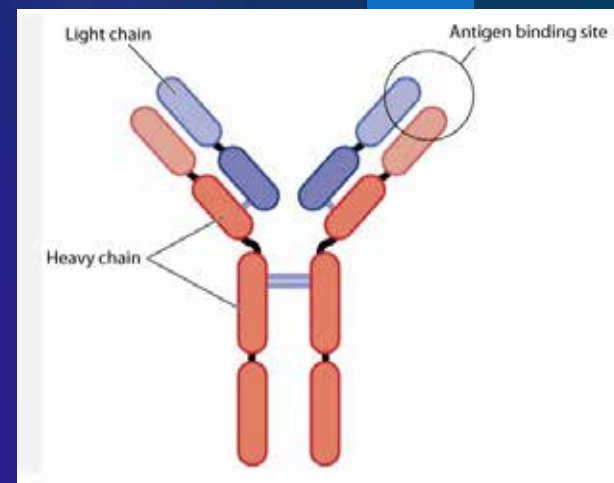


Fig. 1 | **Therapeutic targets in systemic lupus erythematosus.** Various immune cells and molecules interact during the pathogenesis of systemic lupus erythematosus and are the target of monoclonal antibodies and other treatments that have the potential to offer therapeutic advantage. *The mechanism of action of rigerimod is not fully elucidated. APC, antigen-presenting cell; BAFF, B cell-activating factor; BAFFR, BAFF receptor; BCR, B cell receptor; BTK, tyrosine-protein kinase BTK; CD40L, CD40 ligand; FcR, Fc receptor; ICOS, inducible T cell co-stimulator; ICOSL, ICOS ligand; IFNAR, type I interferon receptor; JAK, Janus kinase; TCR, T cell receptor.

Monoclonal antibody structure



Clinical Trial: Steps for drug approval

- Pre-clinical studies – Non-Human
- Phase I studies – 1st time in humans <100 people
 - What are the side effects and what dose should be given?
- Phase II studies – 100+ people
 - Does the drug work and are there other side effects?
- Phase III studies – 1000+ people
 - Does the drug work and is it safe long term?

Targets Interferon pathway—a key player in causing lupus inflammation

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Trial of Anifrolumab in Active Systemic Lupus Erythematosus

E.F. Morand, R. Furie, Y. Tanaka, I.N. Bruce, A.D. Askanase, C. Richez, S.-C. Bae, P.Z. Brohawn, L. Pineda, A. Berglind, and R. Tummala, for the TULIP-2 Trial Investigators*

THE NEW ENGLAND JOURNAL of MEDICINE

Anifrolumab for Systemic Lupus Erythematosus

MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL

362 Patients with moderately to severely active SLE

Anifrolumab

300 mg every 4 wk for 48 wk
(N=180)

Placebo

(N=182)

Response at 52 wk
(British Isles Composite Lupus Assessment)

47.8%

31.5%

Difference, 16.3 percentage points;
95% CI, 6.3 to 26.3; P=0.001

More patients had a response to anifrolumab than placebo, in contrast to results of similar trial with different primary end point

Primary outcomes: Evaluated a lupus disease activity measure called the BICLA

Greater improvements in treatment group of 48 % vs 32 % in placebo

Other outcomes:

-52% vs 30% Patients were able to lower steroid use to less than 7.5 mg daily

Anifrolumab (Saphnelo) for SLE (non-renal lupus)

- ▶ Monthly intravenous infusion
- ▶ Often added on with other lupus treatments such as hydroxychloroquine
- ▶ Effective for cutaneous lupus and arthritis
- ▶ Currently approved for non –renal lupus, but trials to evaluate efficacy in renal lupus are currently ongoing
- ▶ Potential risks-higher rate of herpes zoster in the treatment group

Belimumab (Benlysta) for Lupus Nephritis

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

Richard Furie, M.D., Brad H. Rovin, M.D., Frédéric Houssiau, M.D., Ph.D., Ana Malvar, M.D., Y.K. Onno Teng, M.D., Ph.D., Gabriel Contreras, M.D., M.P.H., Zahir Amoura, M.D., Xueqing Yu, M.D., Chi-Chiu Mok, M.D., Mittermayer B. Santiago, M.D., Amit Saxena, M.D., Yulia Green, M.D., Beulah Ji, M.D., Christi Kleoudis, M.P.H., Susan W. Burris, M.S., Carly Barnett, M.P.H., and David A. Roth, M.D.

Benlysta initially approved for non kidney lupus in 2011

Phase 3, two year trial looking at addition of benlysta to standard care treatment for lupus nephritis

Modest but significant benefits in preventing lupus nephritis flare and worsening kidney function

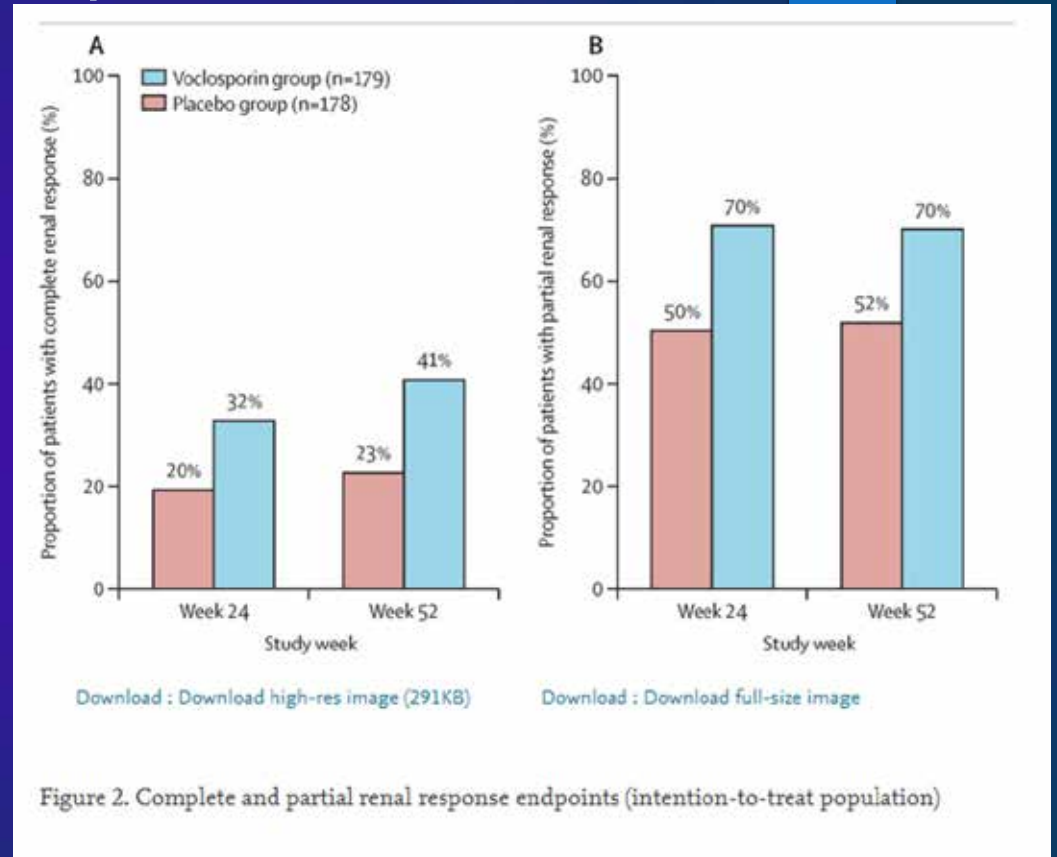
Pretty safe

Monthly intravenous infusion

Can help with other lupus symptoms such as arthritis and rashes

Voclosporin (Lupkynis) for lupus nephritis

- ▶ Approved for add on to standard of care treatment in Lupus Nephritis
- ▶ A type of calcineurin inhibitor (similar to cyclosporine and tacrolimus)
- ▶ Oral tablet (3 tablets twice a day)
- ▶ Effective for reducing protein in the urine rapidly (thought to be associated with better kidney function outcomes)
- ▶ Limits: May not be a good option for someone who has a lot of other lupus symptoms besides kidney disease and not for patients with reduced GFR (or elevated creatinine)



Belimumab (benlysta)	Anifrolumab (saphnelo)	Voclosporin (Lupkynis)
Monthly IV or weekly self injection	Monthly IV infusion	Oral tablets
Approved for Systemic Lupus since 2011, recently also for renal (kidney)lupus	Approved for non-renal lupus. Not yet approved for renal SLE but early trial results are promising	Approved only for renal lupus. Not effective for extra-renal disease
Can be added lupus symptoms refractory to medications, may be added on for newly diagnosed lupus nephritis	For refractory non-renal SLE symptoms such as rashes and arthritis	Best to consider for someone with lupus nephritis with persistent high levels of protein in the urine but normal kidney function

Potential new therapies on the horizon

- ▶ B cell target: Obinutuzumab (Infusion)
 - ▶ Monoclonal antibody against B cells (similar to Rituximab)
 - ▶ *ongoing REGENCY trial here at U of R examining efficacy in lupus nephritis
- ▶ Cenerimod (tablet) in phase 3 trials
 - ▶ Inhibits trafficking of autoreactive T and B cells to the circulation (and other tissues)
- ▶ Litifilimab (injection)
 - ▶ targets a receptor on dendritic cells—a key immune player in lupus
 - ▶ TOPAZ trial currently looking for lupus patients with active disease (URMC is one of the sites)
- ▶ CAR T cell therapy for very severe multi-organ refractory disease

Other adjunctive therapies

- ▶ SGLT2 inhibitors: Inhibitors of sodium glucose transporter (receptor in the kidney)
- ▶ Canagliflozin (Invokana), Dapagliflozin, Empagliflozin
- ▶ Currently available for treatment of type 2 diabetes
- ▶ Have been shown to reduce risk of stroke and heart attack and prevent progression of kidney disease
- ▶ May be of benefit in patients with lupus nephritis (not yet formally studied)

Challenges in finding new lupus treatments

- ▶ Lupus is a heterogenous disease with many variable symptoms
- ▶ Challenging to capture improvements in disease activity—determining the best endpoints of a study is challenging with lupus
- ▶ Large numbers of patients are needed to determine statistical effect
- ▶ Under-representation of minorities-We need better representation from minorities

Currently enrolling clinical trials at UPMC

MiSLE study: Mesenchymal stem cell infusion

- A single infusion of stem cells added on to baseline therapy (certain exclusions)

REGENCY Study: Phase III Randomized Double Blind Placebo Controlled Multicenter Study to Evaluate the Efficacy and Safety of Obinutuzumab in Patients with Lupus Nephritis ---Biologic drug or placebo added on to standard of care therapy (cellcept and steroids)

TOPAZ study Phase 3 study examining drug BIIBO59 (lifitegrast) compared to placebo



Thank You!