



RhAPP

RHEUMATOLOGY ADVANCED
PRACTICE PROVIDERS

RHAPP NATIONAL CONFERENCE

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Advanced Lupus Track

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Disclosures

- Consultant
 - GSK
 - Astra Zeneca

Objectives

- Review autoimmunity mechanisms
- Review specific immune dysregulation to SLE
- Review how medication work on the immune system
- Discuss 2 case scenarios

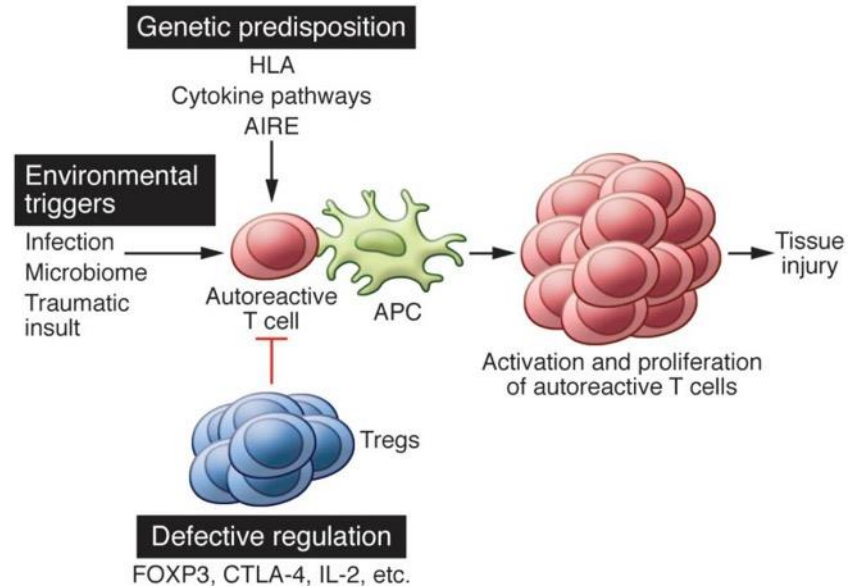


Immune Dysregulation and SLE

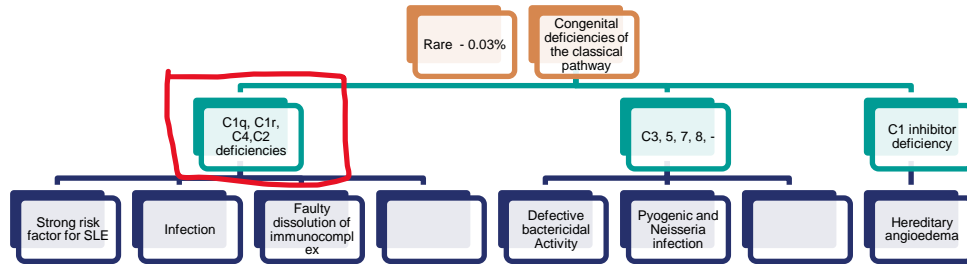


Autoimmunity

- Imbalance between effector and regulatory responses
- Defective elimination and or control of self-reactive Lymphocytes
 - Cannot distinct self from foreign
- Combination of genetic predisposition, environmental triggers and hormone
- Dysbiosis



Complement Deficiencies



SLE –
• classical pathway

ANCA Vasculitis
• alternative pathway
• C4 deficiency

Antiphospholipid Syndrome
• Alternative Pathway
• C3/C4 low plasma levels

Membranous Nephropathy
• Lectin pathways

Interferon Alpha and SLE

Elevated IFN- α

SLE serum induces IFNGS (type I interferon gene signature)

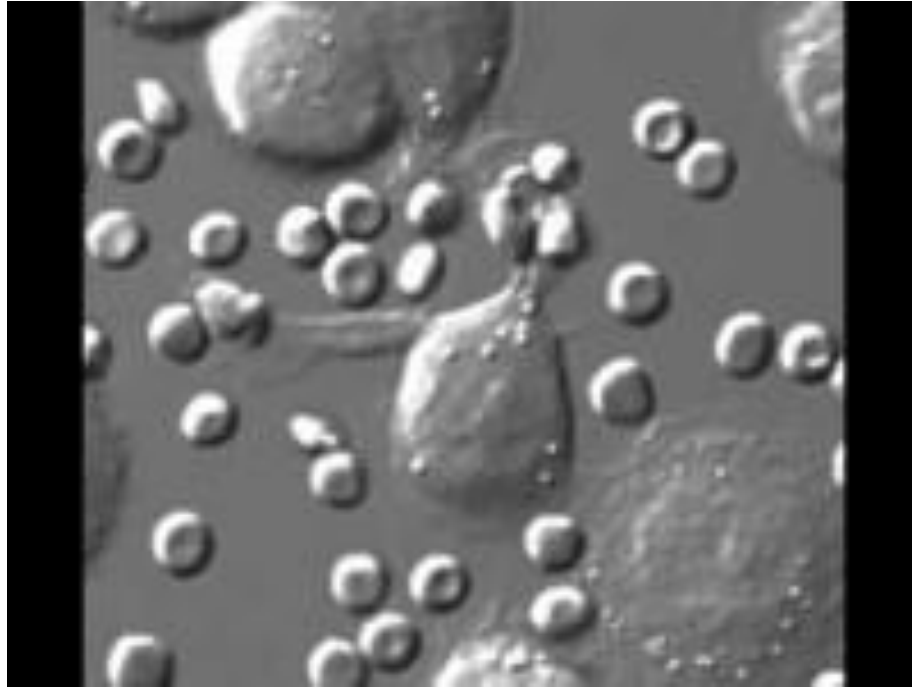
60% -75% of SLE pt are IFNGS positive

Clinical and serologic activity correlate with IFN gene expression

Indie

- Indirect and Direct Targets
 - DNA
 - Immune complexes
 - RNA
 - TLR
 - Hydroxychloroquine
 - pDC
 - Type I interferons
 - Type II interferons
 - JAK/STAT

The Garbage Truck



B Cell Involvement

Production of autoantibodies

Release of cytokines and chemokines, including IL-6, IL-10, and others

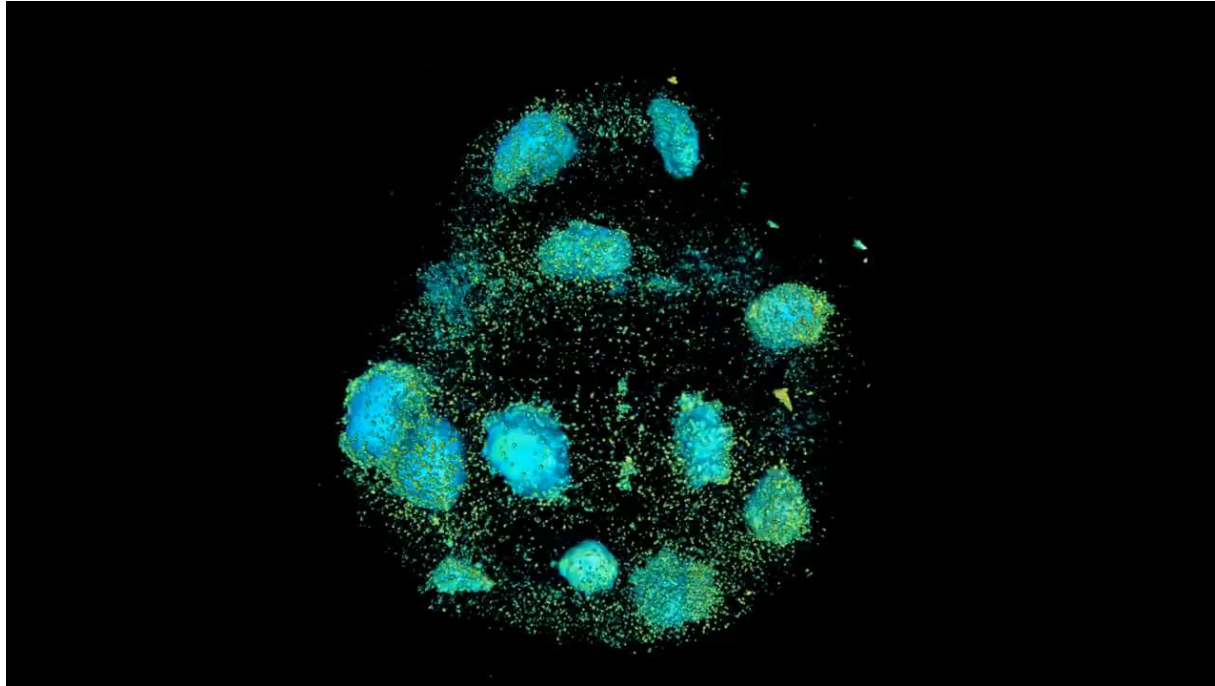
Antigen presentation to T cells

Deposition of immune-complexes in the rheumatoid synovium¹

Induction of tissue damage by anti-cyclic citrullinated peptide (CCP) autoantibodies²

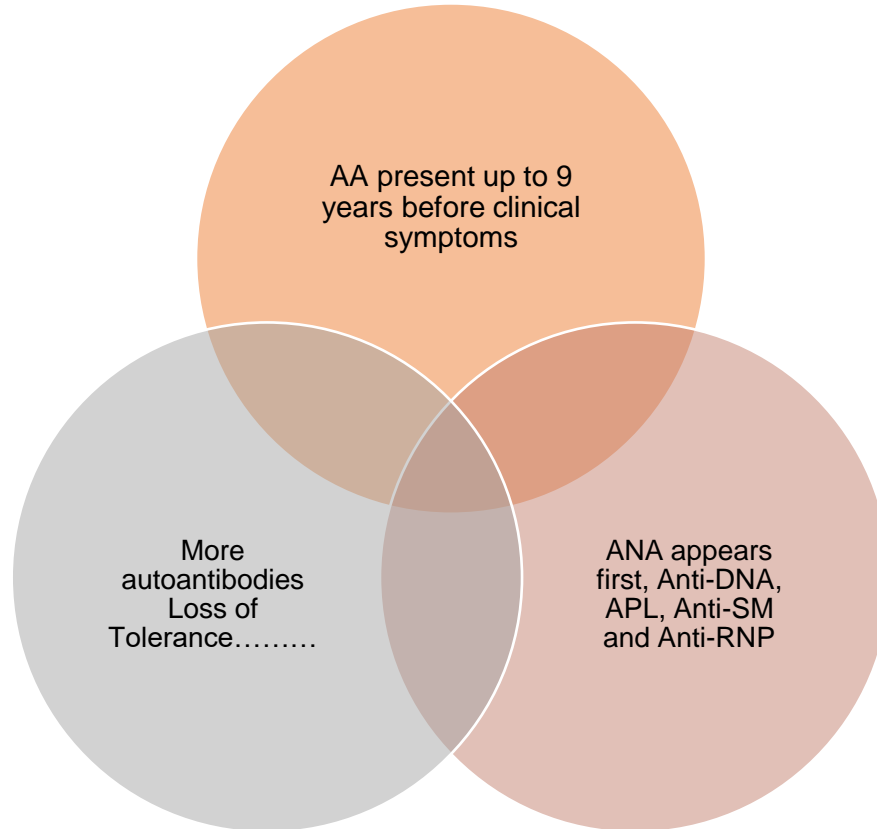
B-cell depletion is associated with a reduction in autoantibody formation and disease improvement

The TSA Agent

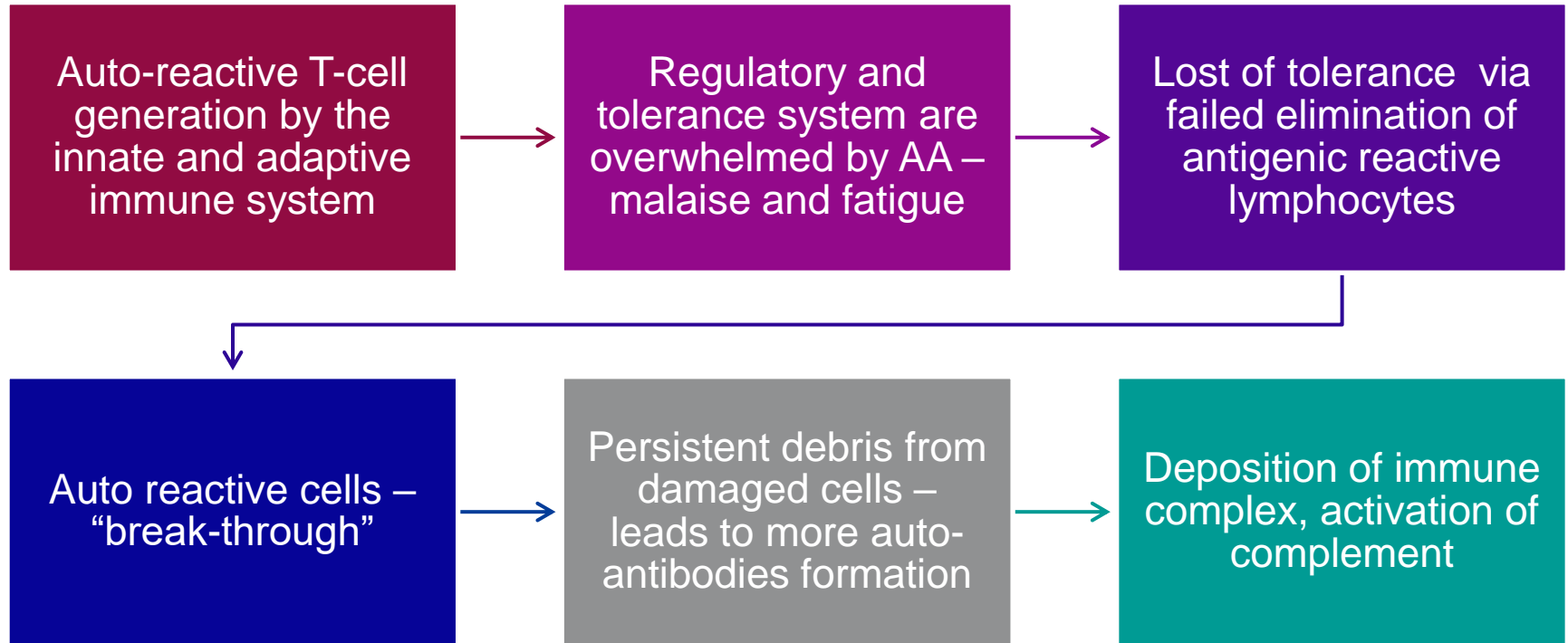


Stoler-Barak, L., Biram, A., Davidzohn, N., Addadi, Y., Golani, O., & Shulman, Z. B cell dissemination patterns during the germinal center reaction revealed by whole-organ imaging. *Journal of Experimental Medicine*. 2019. 216(11), 2515-2530.

The Calm Before the Storm Benign Autoimmunity



The Garbage Truck, the TSA Agent and the Block Party





Treatments of SLE



The Lupus Arsenal

1894 – Quinine, salicylates (prostaglandins)

1952 – Acthar Gel (hormone – same as prednisone)-

1954 – Prednisone(suppress migration of Leukocytes – aka macrophages)

1955 – Hydroxychloroquine – reduces pro-inflammatory cytokine

1970's – Azathioprine (off label) – (T cell)

1988 – Methotrexate (MTX) – reduces antigen-dependent T cell proliferation and suppress inflammation

1990's – Mycophenolate MMF (lupus nephritis only) (B and T cell)

2010 – Cyclophosphamide (CYC) – cytotoxic agent

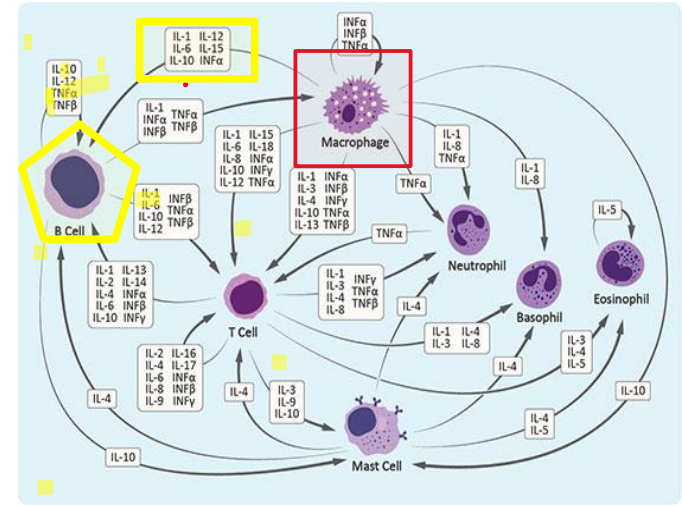
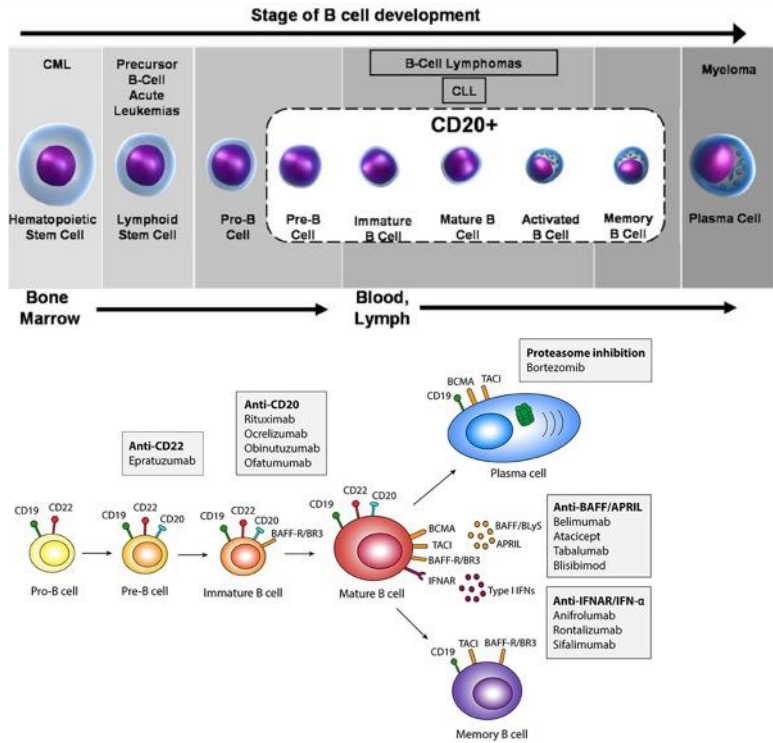
2011 – Belimumab - B lymphocyte stimulator (BLyS), also known as B-cell activating factor (BAFF)

Rituximab (RTX) – off label (CD20 - B cell)

Voclosporin 2020 - antigen-dependent cytotoxic T lymphocytes

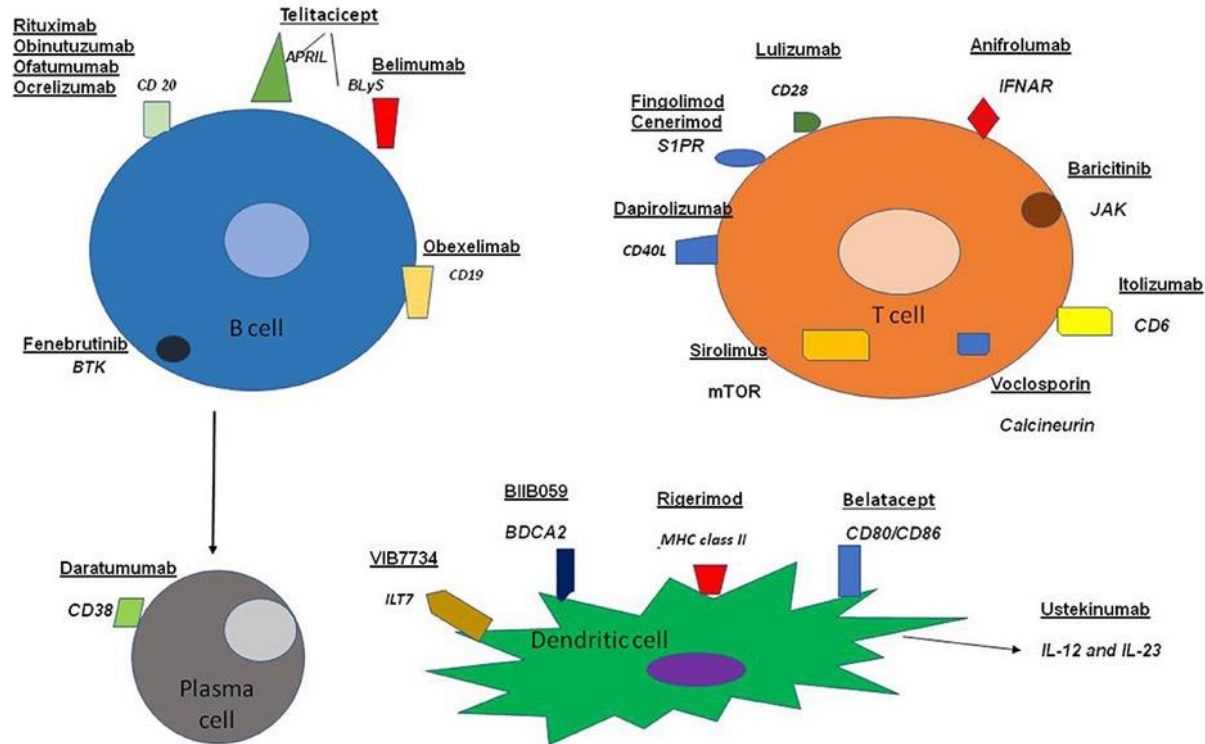
Saphnelo - type 1 Interferon

Soo Many Targets



van Meerten, T., & Hagenbeek, A. CD20-targeted therapy: the next generation of antibodies. In *Seminars in hematology*. 2010, April. Vol. 47, No. 2, pp. 199-210; WB Saunders. Cytokine's and their detection. *Enzo life sciences*; Parodis, I., Stockfelt, M., & Sjöwall, C. B cell therapy in systemic lupus erythematosus: from rationale to clinical practice. *Frontiers in Medicine*. 2020. 7, 316.

Molecules Targeted Therapeutically in Patients With SLE



Target Cell Approach

Drug	Mechanism of action	Phase of the study	Manifestation	Primary outcome
Obinutuzumab	Anti-CD20 mAb: causes B cell depletion	II	Lupus nephritis	Complete renal response at week 52
Obexelimab	Anti-CD19 mAb: inhibits B cell activation	II	SLE	Loss of improvement at day 225
Belatacept	CTLA4-IgG1: blocks T cell costimulation	Retrospective	Lupus nephritis following renal transplantation	
Lulizumab	Anti-CD28 mAb: inhibits T cell activation	II	SLE	Proportion of responders using BILAG-BICLA at day 169
Rigerimod or Lupuzor	Peptide-fragment of the small ribonucleoprotein U1-70K: Inhibits T cell reactivity through binding to MHC class II	III	SLE	SRI response at week 52
Daratumumab	Anti-CD38 mAb: causes plasma cell depletion	Case report	SLE and lupus nephritis	
VIB7734	mAb: binds to ILT7 of pDCs resulting in their elimination	I	SLE Sjogren's and CLE	
BIIB059	mAb: binds to BDCA2 receptor of pDCs, inhibiting thereby the production of IFN-1	II	SLE (part A) CLE (part B)	Change in total active joint count from baseline to week 24 CLASI-A at week 16

Cytokine Approach

Drug	Mechanism of action	Phase of the study	Manifestation	Primary outcome
Belimumab	mAb that targets BLYS: inhibits B cell survival	FDA approved	Lupus nephritis	Primary efficacy renal response
Telitacicept	TACI-Fc fusion protein that targets BLYS and APRIL: inhibits development and survival of mature B cells and plasma cells	2b	SLE	SRI-4 response at week 48
Anifrolumab	mAb that binds to IFN-I receptor: blocks the activity of type I interferons	III	SLE	BICLA response at week 52
Ustekinumab	mAb that binds to p40 subunit of IL-12 and IL-23	II	SLE	SRI-4 response at week 24
Low dose of IL-2	Restoration of immune tolerance		SLE and lupus nephritis	SRI-4 response at week 12

Intracellular Molecules

Drug	Mechanism of action	Phase of the study	Manifestation	Primary outcome
Voclosporin	Calcineurin inhibitions	FDA approved	Lupus nephritis	Complete renal response
Sirolimus	mTOR inhibition	1/2 Retrospective	SLE Lupus nephritis	Decrease in SLEDAI and BILAG scores at each visit (months 1–12)
Baricitinib	JAK1 and JAK2 inhibitor	II	SLE	SLEDAI-2K at week 24
Mepacrine	Unknown	Retrospective analysis of the prospectively acquired data	SLE	

BTK Inhibitors, JAK Inhibitors, and Other Agents

BTK inhibitors	JAK inhibitors	Miscellaneous
Fenebrutinib (GDC-0853) (63)	Upadacitinib (JAK1 inhibitor) (64)	Lenabasum (JBT-101) (endocannabinoid type 2 receptor agonist) (65)
Orelabrutinib (ICP-022) (66)	Tofacitinib (JAK1, JAK3, JAK2 inhibitor) (67)	Memantine (NMDA receptor antagonist) (68)
Branebutinib (69)	PF-06700841 or Brepocitinib (JAK1, TYK2 inhibitor) (70)	EBV-specific cytotoxic T lymphocytes (71)
Elsubrutinib (64)	BMS-986165 or Deucravacitinib (TYK2 inhibitor) (72)	Mesenchymal stem cells in A) SLE (73) B) Lupus nephritis (74) Curcumin (75)

Case Study 1

- 20-year-old male diagnosed with SLE 1 year ago presenting with fatigue, weight loss, joint pain
- 1 hospital admission for pericarditis
- Current medication methotrexate 15 mg weekly with folic acid and hydroxychloroquine 400 g daily
- Physical examination
 - Cachectic
 - Tachypneic
 - Jaw lock
 - Atrial flutter on ekg
 - Weight loss of over 80 lbs

Labs

- Before hydration
 - dsDNA > 1000, positive SM and RNP
 - Hg 10
 - Urine concentration 1,050
 - Protein 0.4
 - C4:10
- After hydration
 - Hg 7
 - Proteinuria 1G
 - C4: 3



What Would You Do?

Case Study 2

- 12-year-old AA female – presenting with fever mucositis and arthritis
- Started on HCQ and steroids
- Labs
 - DsDNA, complementemia (C3 and c4), smith and RNP
- Started on azathioprine for persistent leukopenia – stopped due to no response – started on mycophenolate – terrible non-compliance
- Ongoing leukopenia and anemia
- Transfer to adult ambulatory care at 20

Case Study 2 – Continues

- Switched to belimumab injections – patient was going away for college. Mycophenolate was stopped. She continues with HCQ and eventually labs normalized, and prednisone was stopped.
- Lost to follow-up for 10 months – reports taking HCQ and prednisone as needed for joint pain – taking belimumab maybe once a month
- Admitted to the hospital with severe abdominal pain
 - 2020 – Diagnosed with lupus enteritis – target sign appearance X 2
 - 2021 – Proteinuria – Biopsy consistent:
 - The biopsy reveals a crescentic and focal necrotizing glomerulonephritis with sparse immune complexes, and minimal chronic changes, in this patient with SLE. Uninvolved glomeruli do not reveal endocapillary hypercellularity, wire-loops, mesangial expansion, or other significant changes. However, more than 50% of all glomeruli reveal segmental necrosis and / or cellular crescents. Recent ANCA serologies were reported as negative. The findings are therefore classified as diffuse proliferative lupus nephritis, class IV-S (A) in the ISN / RPS system.



What Would You Do?

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