UPDATES IN IMMUNOLOGY FOR THE PRIMARY CARE PHYSICIAN

JUNE 24, 2026

Steve Lee, DO FACR
SCPMG Rheumatology

Associate Professor, Western Univ, CUSM, Touro Univ

Assistant Professor, LECOM, Loma Linda Univ

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Disclosures

- Clinical Trial Support:
  - Fate Therapeutics
  - GSK
  - Sanofi
  - Astra Zeneca

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LEARNING OBJECTIVES

- Overview of the Immune System
  - Innate: rapid, nonspecific
  - Adaptive: specific, memory
- Immunopathogenesis of Common Rheumatic Diseases
- Clinical Immunology Markers and their Interpretation (cont on Friday..)
- Implications for Diagnosis and Management in Primary Care

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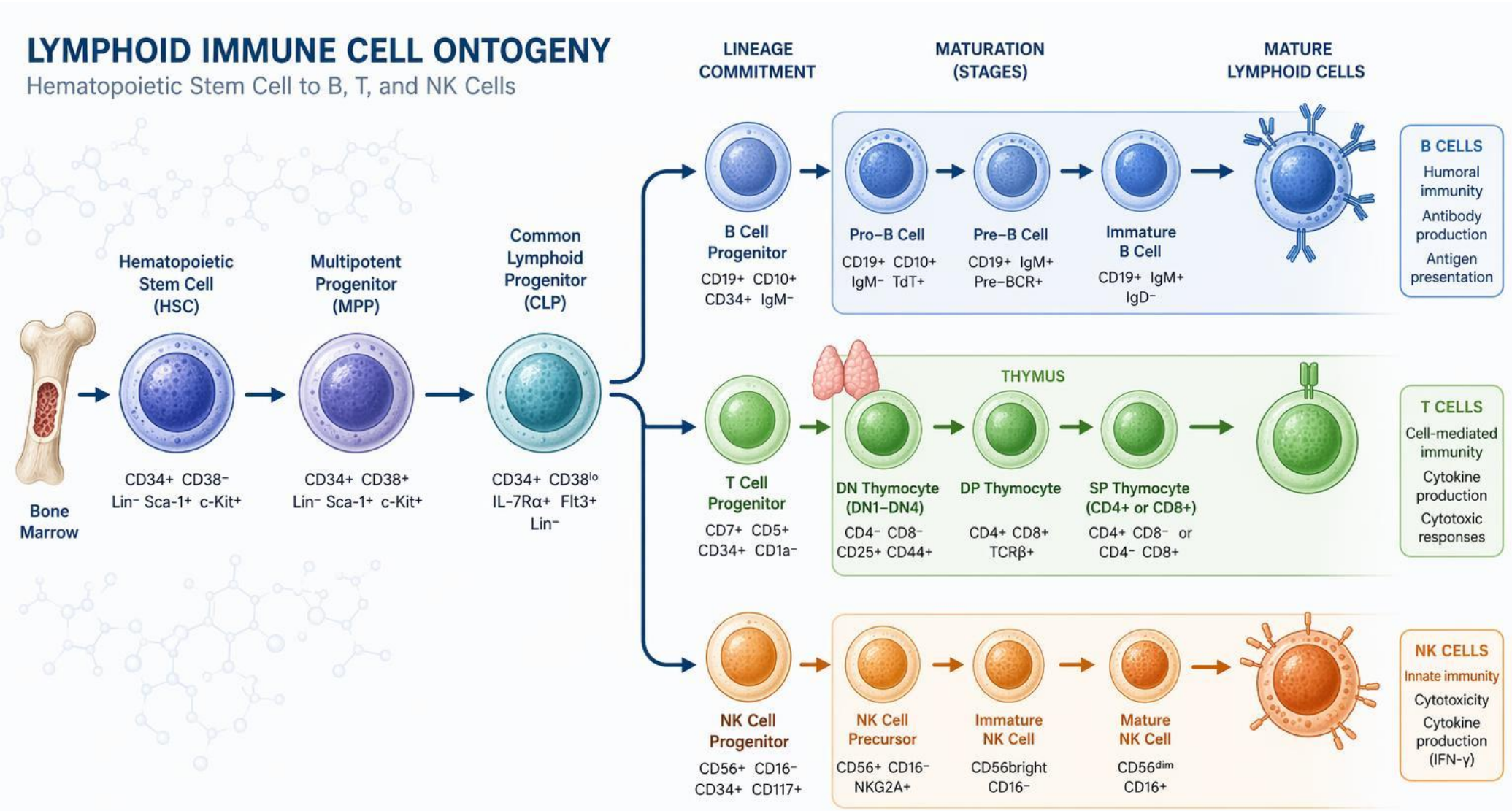
LYMPHOID IMMUNE CELL ONTOGENY

Hematopoietic Stem Cell to B, T, and NK Cells



BCR (B Cell Receptor)
Antigen recognition on B cells

TCR (T Cell Receptor)
Antigen recognition on T cells

NK Receptors
Recognize stressed cells and MHC I expression

Cytotoxic Granules (Perforin, Granzymes)
Mediators of target cell killing

Lineage Progression
Arrows indicate developmental progression

Microenvironment
Cytokines and niches regulate proliferation, survival, and differentiation

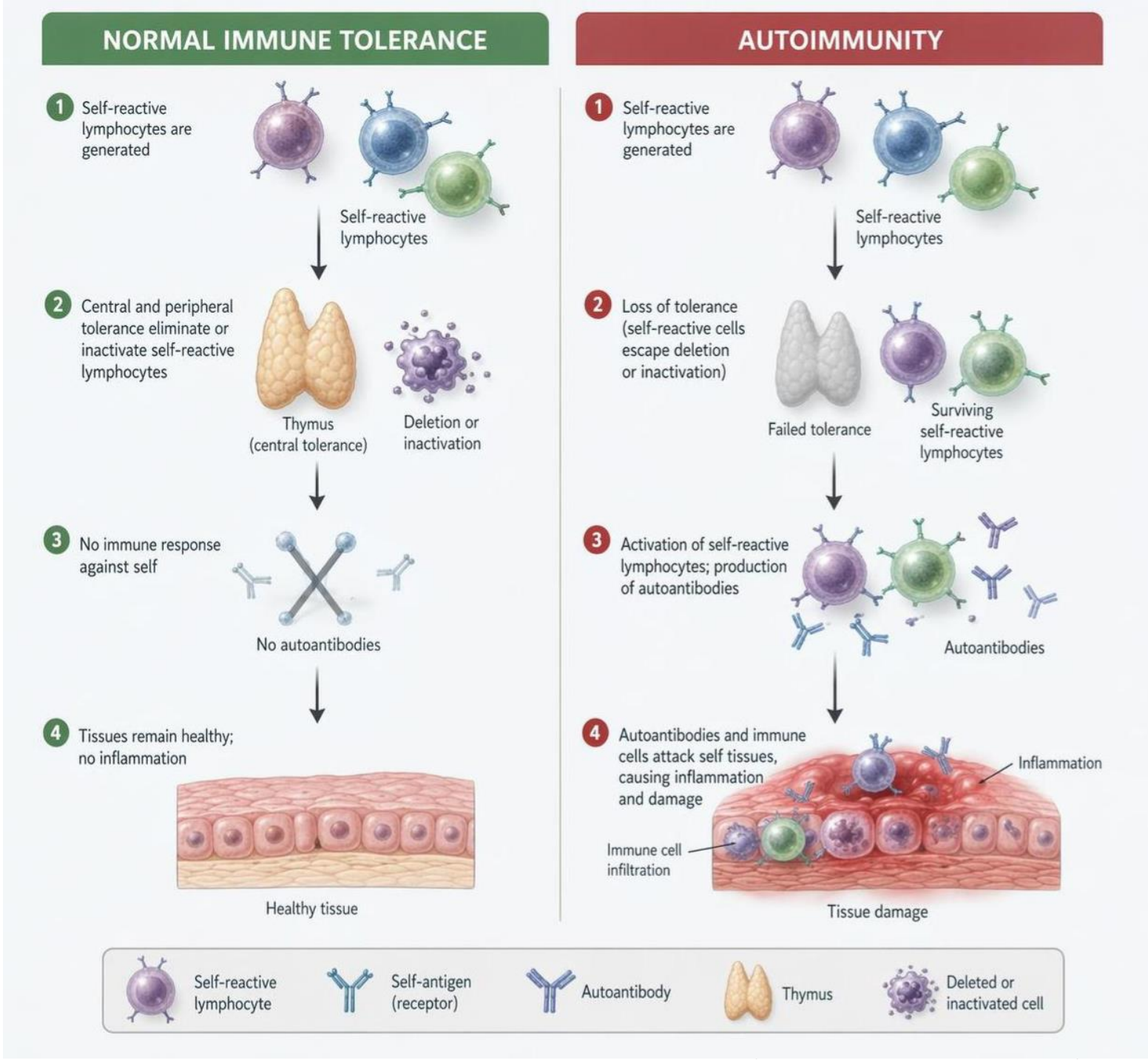
KEY CYTOKINES

- IL-7 – Survival, proliferation (CLP, B, T)
- Flt3L – Progenitor maintenance/expansion
- IL-15 – NK cell development, survival
- SCF – Stem cell maintenance

IMMUNE TOLERANCE:

Normal tolerance: Central/peripheral tolerance restrain self-reactive cells; preserve pathogen defense.

Autoimmunity: Tolerance failure: autoantibodies, autoreactive T cells, immune complexes → chronic inflammation, organ injury. Often starts as episodic, multisystem symptoms pre-diagnosis.



IMMUNE SIGNALING PATHWAYS RELEVANT TO RHEUMATIC DISEASE

Key Cytokines in Rheumatic Disease

TNF-alpha, IL-6 drive inflammation and tissue damage in rheumatic diseases.

Inflammatory Signaling Pathways

These cytokine signaling pathways activate immune cells

Steps contribute to chronic inflammation and damage

JAK-STAT pathway

Therapeutic Implications

Understanding cytokines and pathways enables development of targeted therapies and clinical interventions for rheumatic diseases.

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Q1: WHAT AUTO ANTIBODY IS MOST HIGHLY SPECIFIC FOR THE DETECTION OF RA?

- Anti-ribonucleoprotein (RNP)
- SSA
- Anti-cyclic citrullinated peptide (CCP)
- Rheumatoid factor (RF)
- Anti-tumor necrosis factor (TNF)

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- Rheumatoid factor (RF)
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RATIONALE

- Specificity of anti-cyclic citrullinated peptide antibody (ccp) or anti-citrullinated peptide antibody (ACPA) > Rheumatoid Factor (RF)
- 2010 ACR RA classification provided more specificity for detecting RA
- Both predict severity and extra-articular manifestations

Aletaha. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. Sept; 62(9):2569-81.

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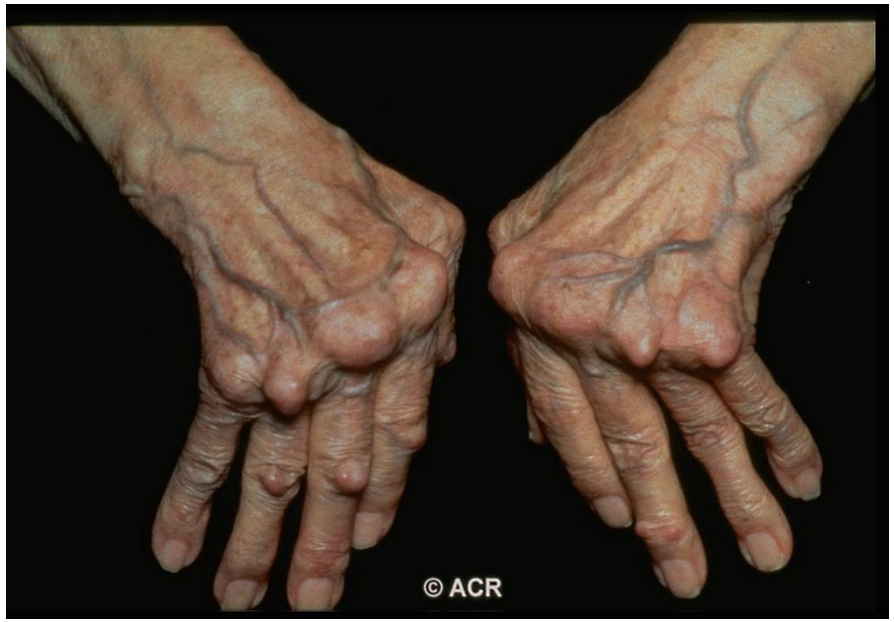
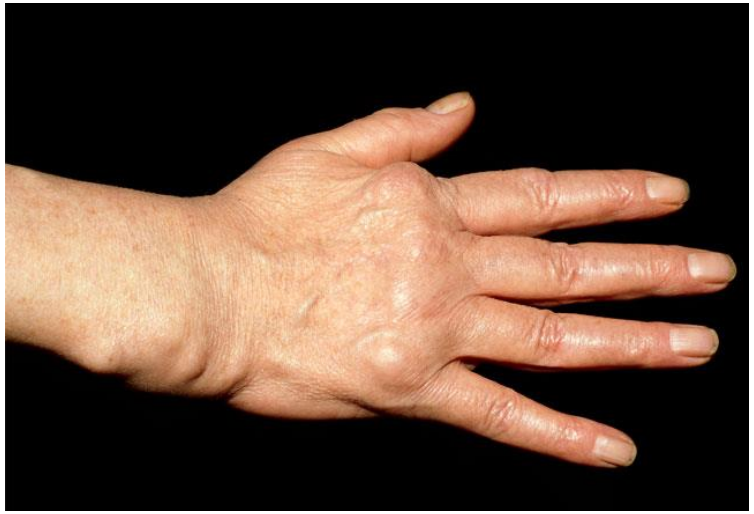
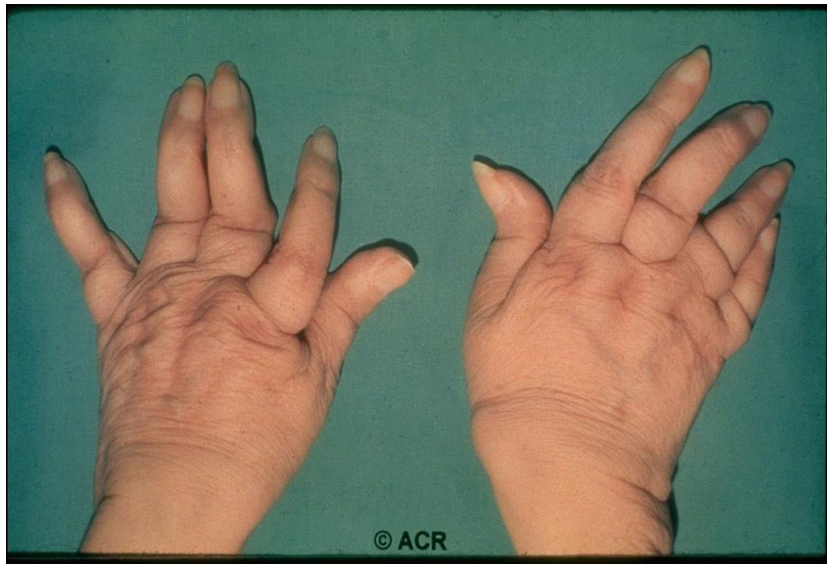
Clinical Features



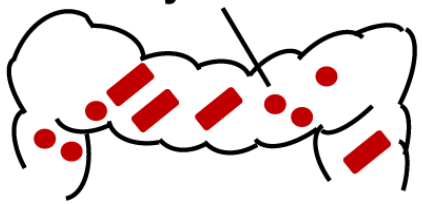




Environmental factors

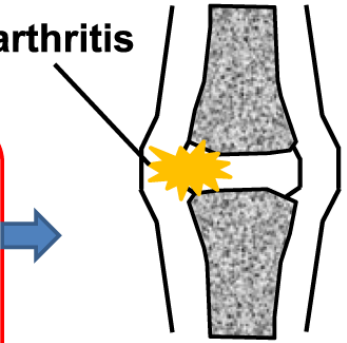
Smoking
Hormones
Infection

dysbiosis



Gut microbiota
Prevotella copri
L. salivarius
Collinsella

arthritis



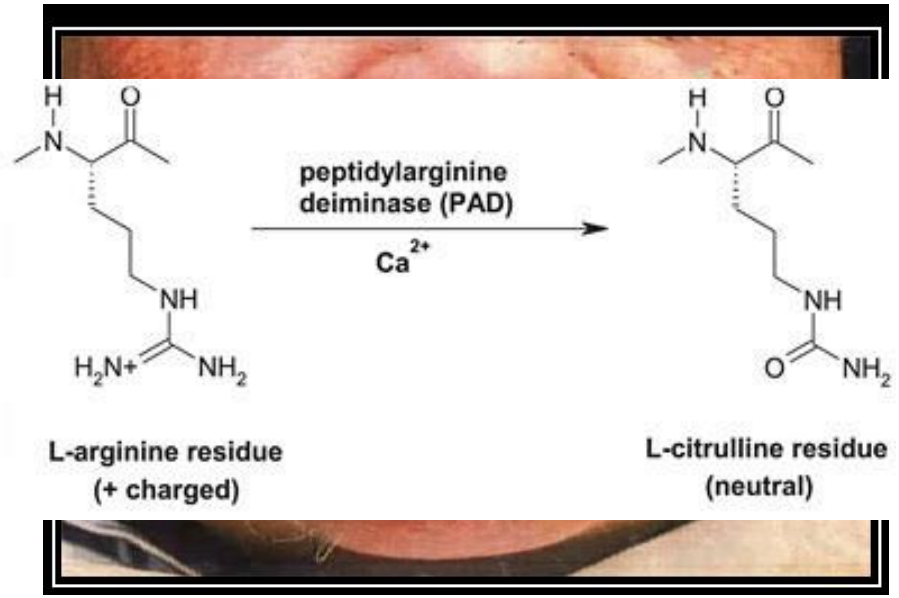
Periodontal bacteria
P. gingivalis
A. actinomycetemcomitans

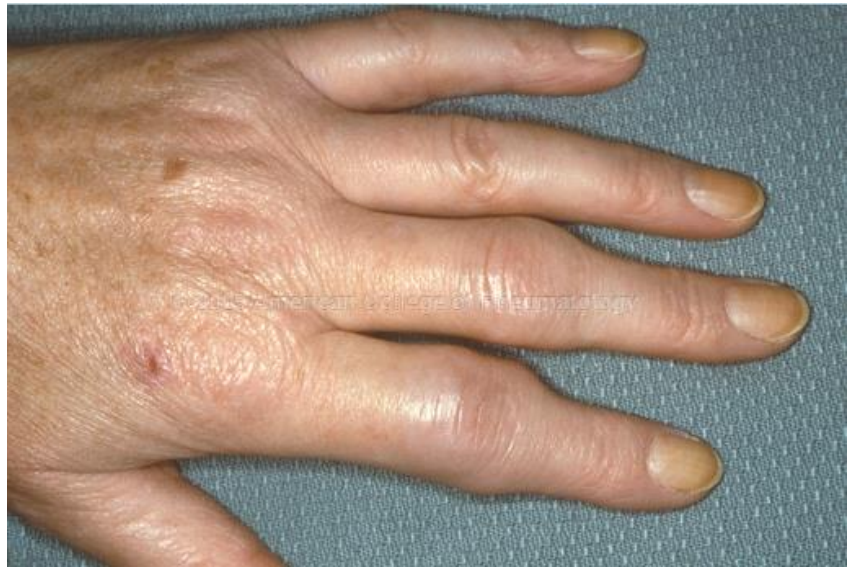
Production of autoantibody (ACPA, RF)

←Healthy→ ←pre-clinical stages→ ←Rheumatoid arthritis→

Genetic backgrounds

・HLA-DRB1 ・PTPN22 etc.





Maeda, Y., Takeda, K. Host–microbiota interactions in rheumatoid arthritis. *Exp Mol Med* **51**, 1–6 (2019).

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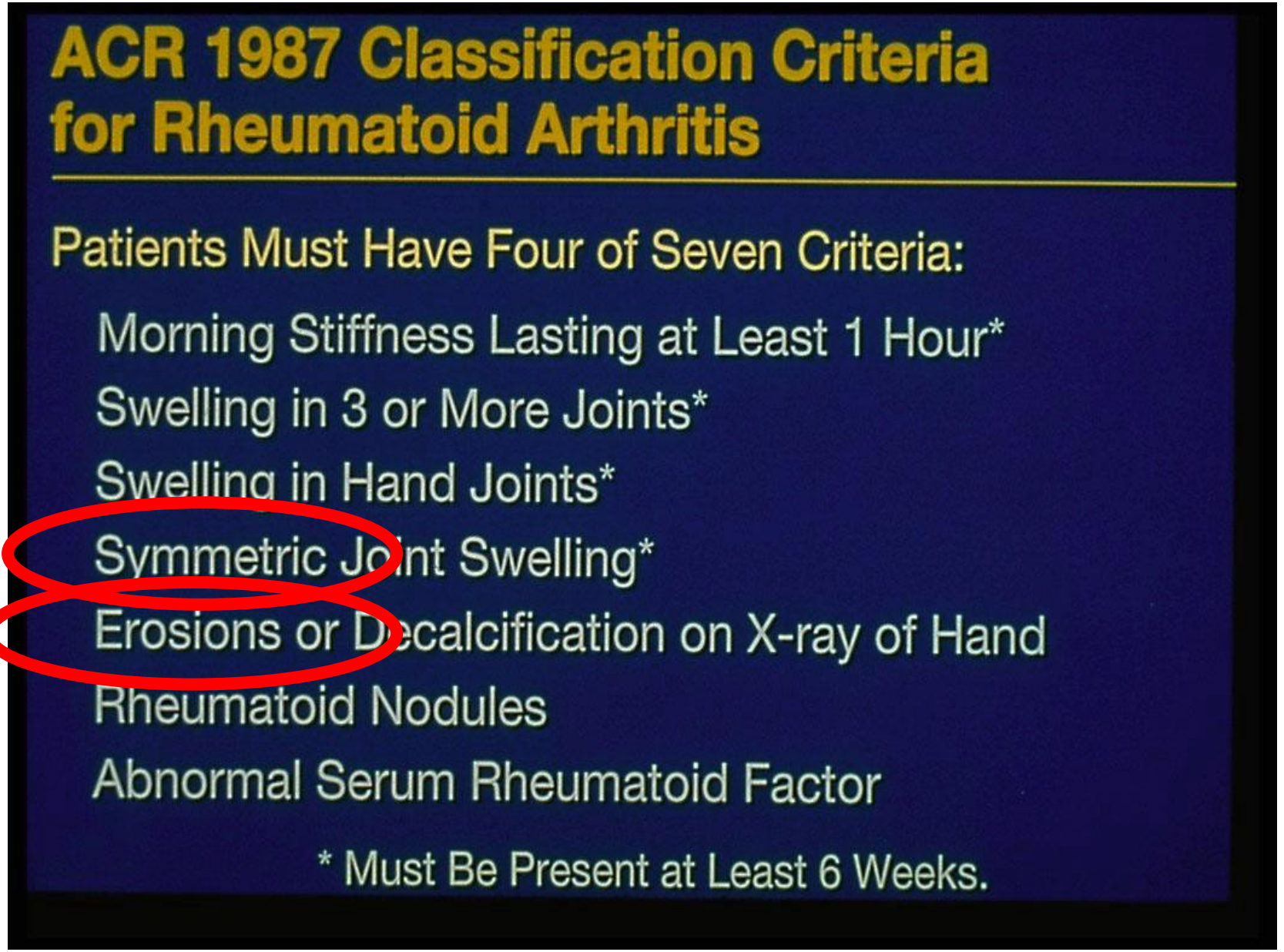

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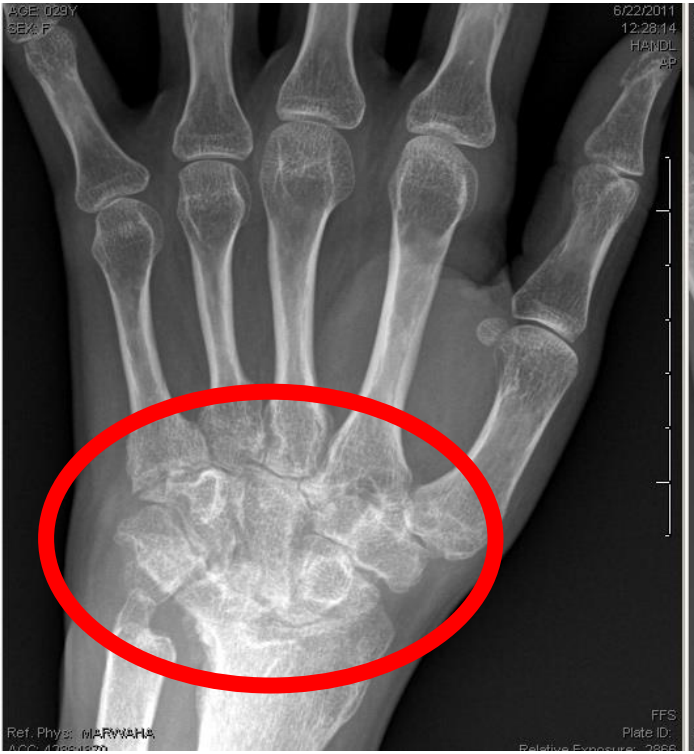

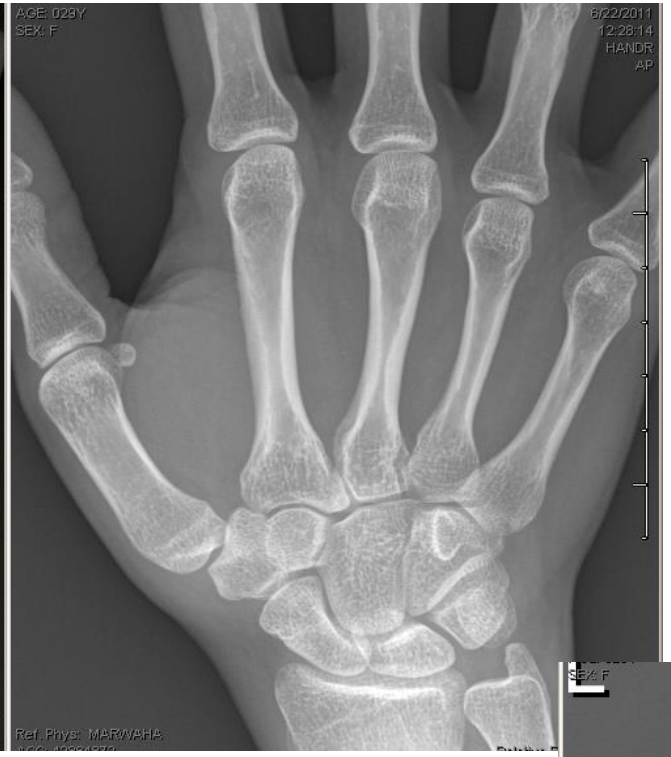

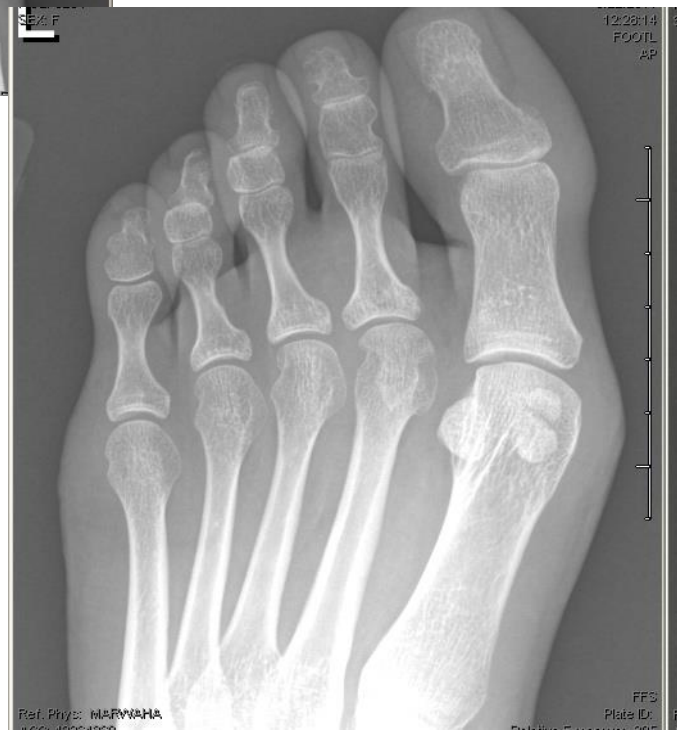

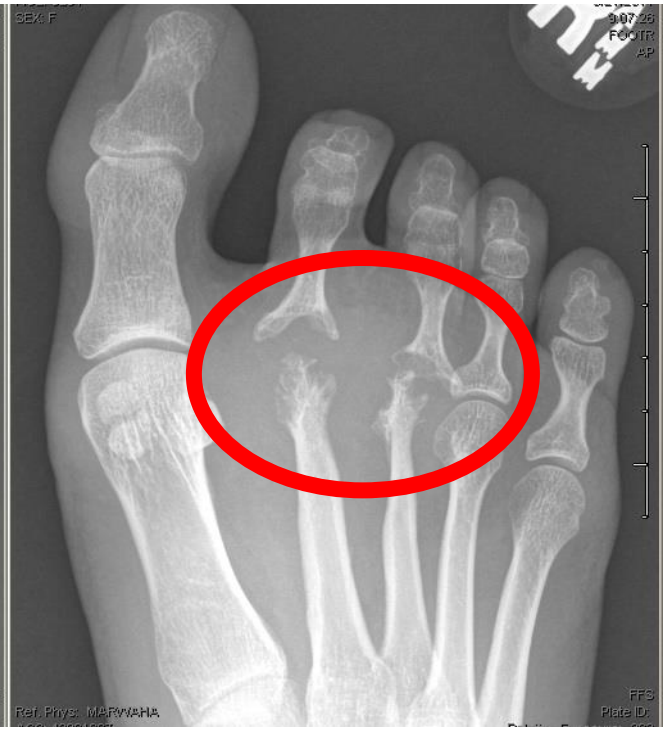

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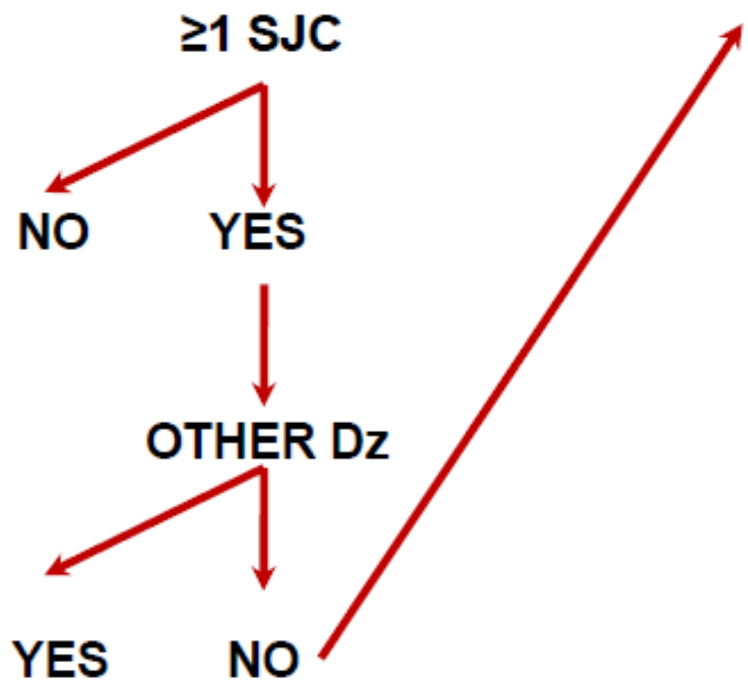
2010 ACR/EULAR RA classification criteria



RA can be classifiable or diagnosed with a score ≥6

JOINT DISTRIBUTION	
1 large joint	0
2–10 large joints	1
1–3 small joints (large joints excluded)	2
4–10 small joints (large joints excluded)	3
>10 joints (at least 1 small joint)	5
SEROLOGY	
Negative RF and negative ACPA	0
Low positive RF or ACPA (≤3x ULN)	2
High positive RF or ACPA (>3x ULN)	3
SYMPTOM DURATION	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

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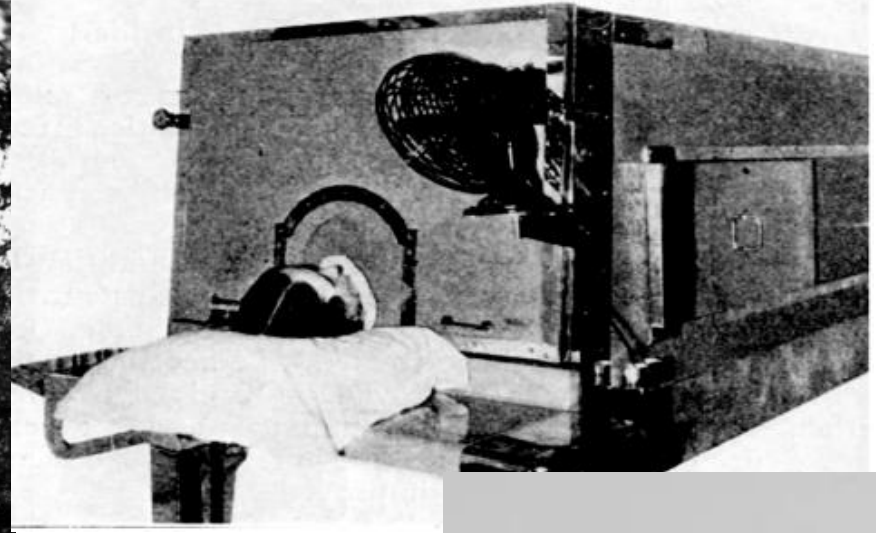

Dr Philip Hench, 1950,
Nobel Prize in medicine

Hunder, GG, Matteson EL. Mayo Clin Proc. Apr 2010

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RA TREATMENT: OPTIMIZING OUTCOMES

- Early diagnosis and risk stratification
- DMARDs early (within 3 mo of symptoms)
- Add biologic or targeted DMARD
- “Treat to Target” – DAS28, RAPID3, CDAI, SDAI
- Steroids
  - bridge to effective DMARD therapy
  - prednisone >10 mg/d rarely needed for joints
  - minimize long term side effects (osteoporosis, DM)
- Co-morbidities
  - atherosclerosis
  - osteoporosis
  - interstitial lung disease

Fraenkl. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care and Research. July 2021

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TRADITIONAL DMARD'S

- methotrexate/Rheumatrex
- leflunomide/Arava
- sulfasalazine/Azulfidine
- azathioprine/Imuran
- hydroxycholoroquine/Plaquenil
- mycophenolate mofetil/Cellcept

- gold
- minocycline
- doxycyline
- penicillamine
- cyclophosphamide
- cyclosporine

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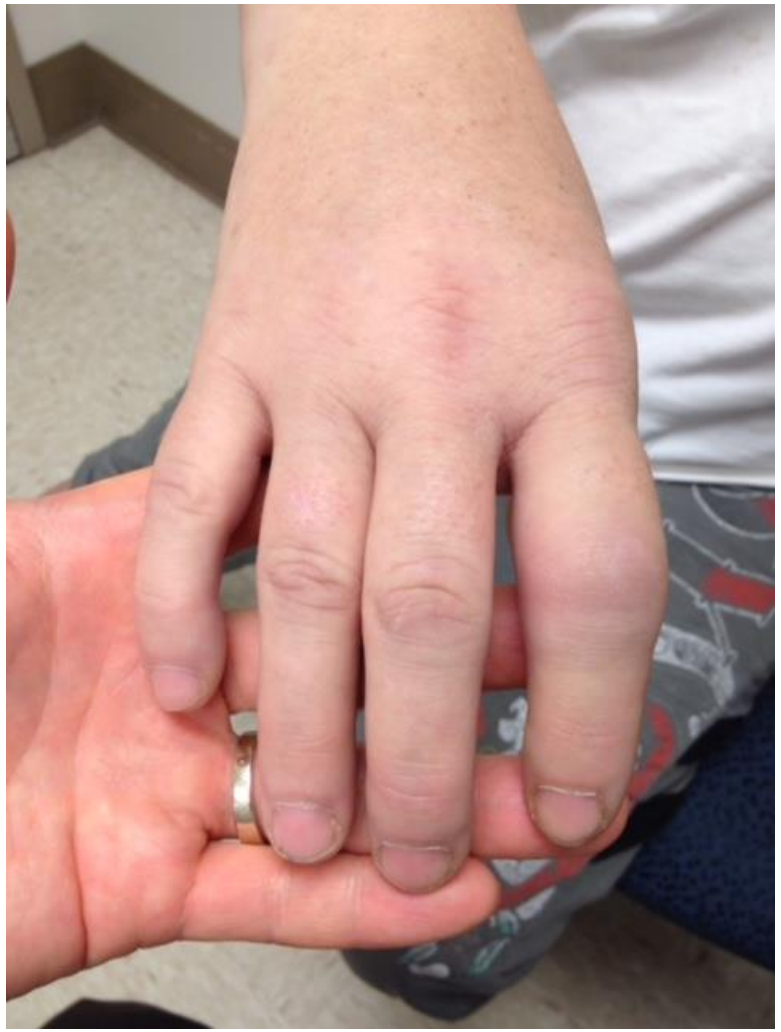
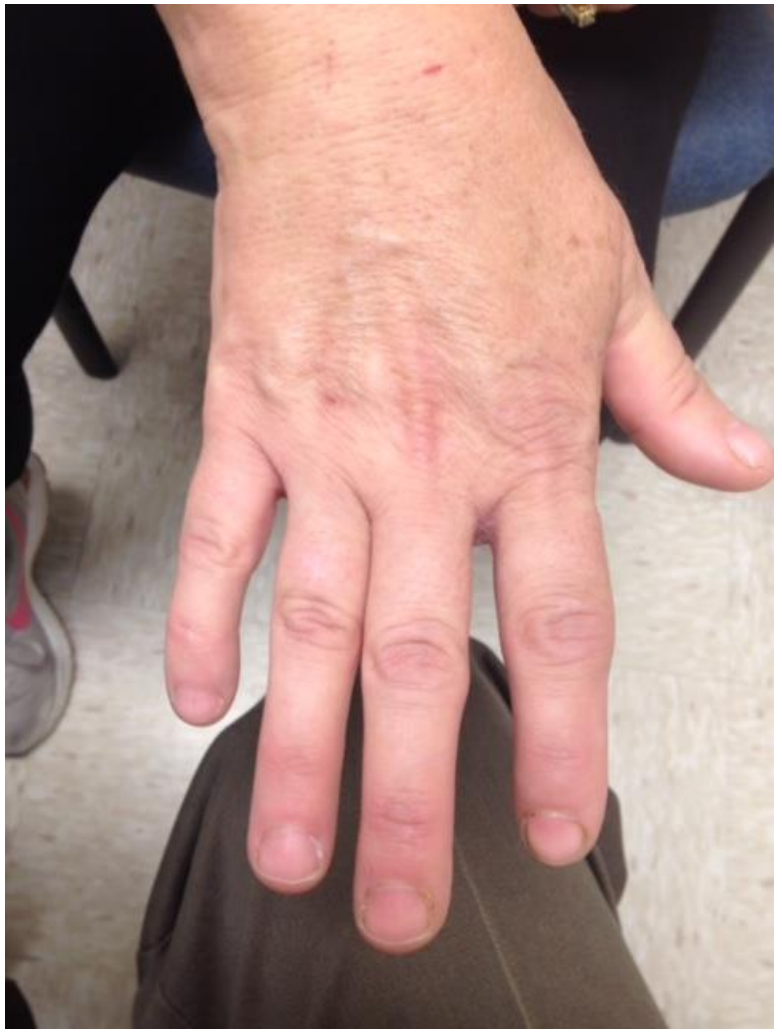
METHOTREXATE





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EXTRA-ARTICULAR MANIFESTATIONS

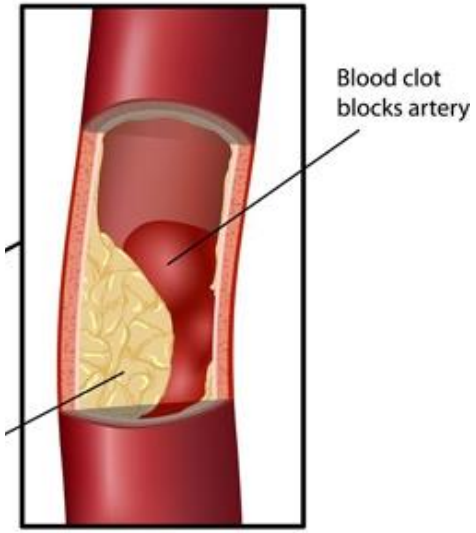
RA: Not Just a Joint Disease

- CVD 10 Years Earlier
- 6-9x ↑ Serious Infections
- 2x ↑ Malignancy
- ↑ Pulmonary Disease
- ↑ GI Bleeding
- Life Expectancy Decreased 10 yr women, 4 yr men

Joint pain
Disability
Destruction

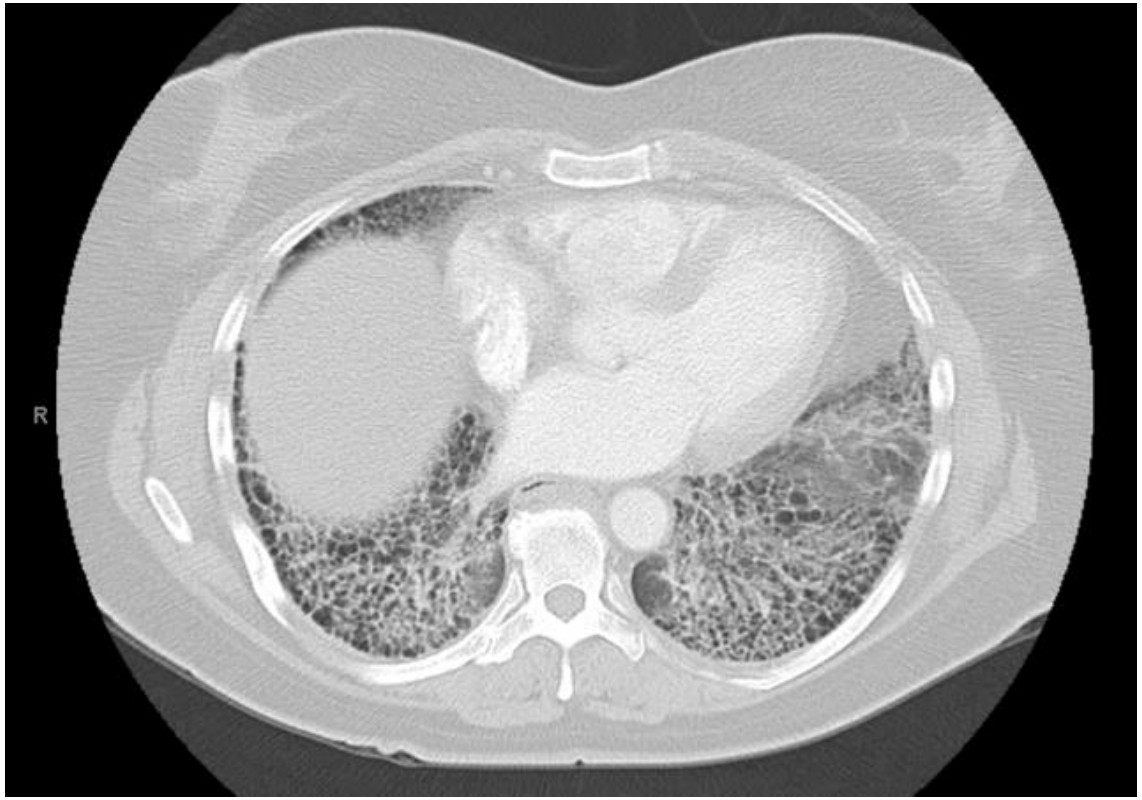
Deane K. *J Musculoskel Med.* 2006;23:S24-S31.

RheumNow



Q2: A 63 year old female with long standing seropositive RA presents to her internist's office with worsening cough and dyspnea for months. No changes of medications for years. Methotrexate, and hydroxychloroquine and prednisone 2 mg QD. Chest CT is obtained
What is the next best step in management of symptoms?

1. Add TMP/SMX DS three times weekly
2. Stop hydroxychloroquine
3. Add nintendanib
4. Switch methotrexate→mycophenolate



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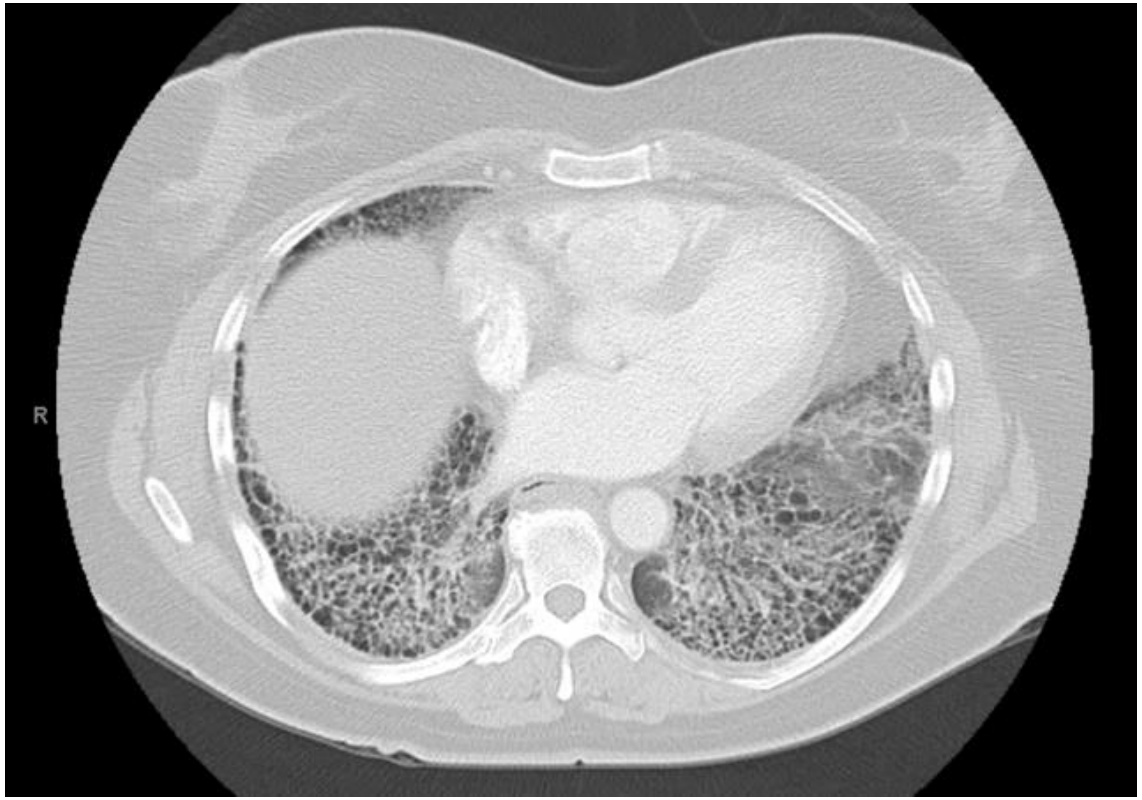

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RATIONALE

- RA patients can have NSIP or UIP
- Hydroxychloroquine is not immunosuppressing
- Anti-fibrotics are later line treatment
- Mycophenolate mofetil is considered 1st line treatment for SARD-ILD
- Rituximab and tocilizumab are also next line treatments

Johnson et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases. Arthritis and Rheum. 2024. pp 1182-1200.

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Arthritis & Rheumatology
Vol. 76, No. 8, August 2024, pp 1201–1213
DOI 10.1002/art.42860
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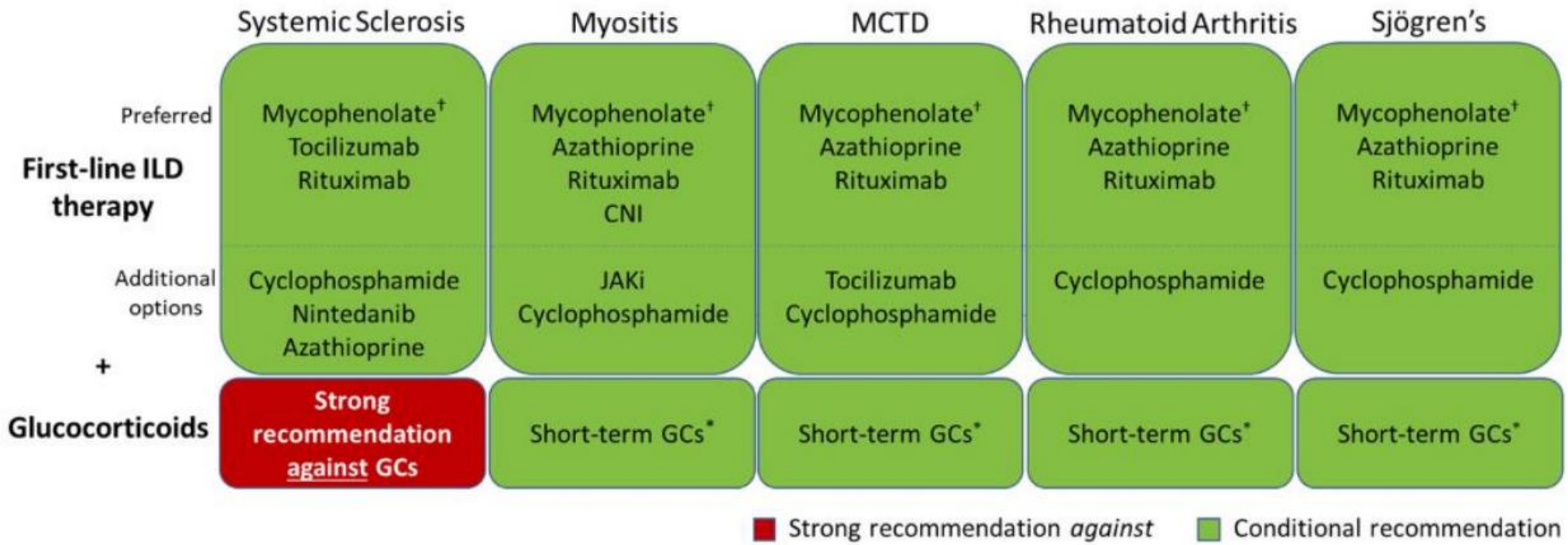
American College of Rheumatology
Empowering Rheumatology Professionals

2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Screening and Monitoring of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases



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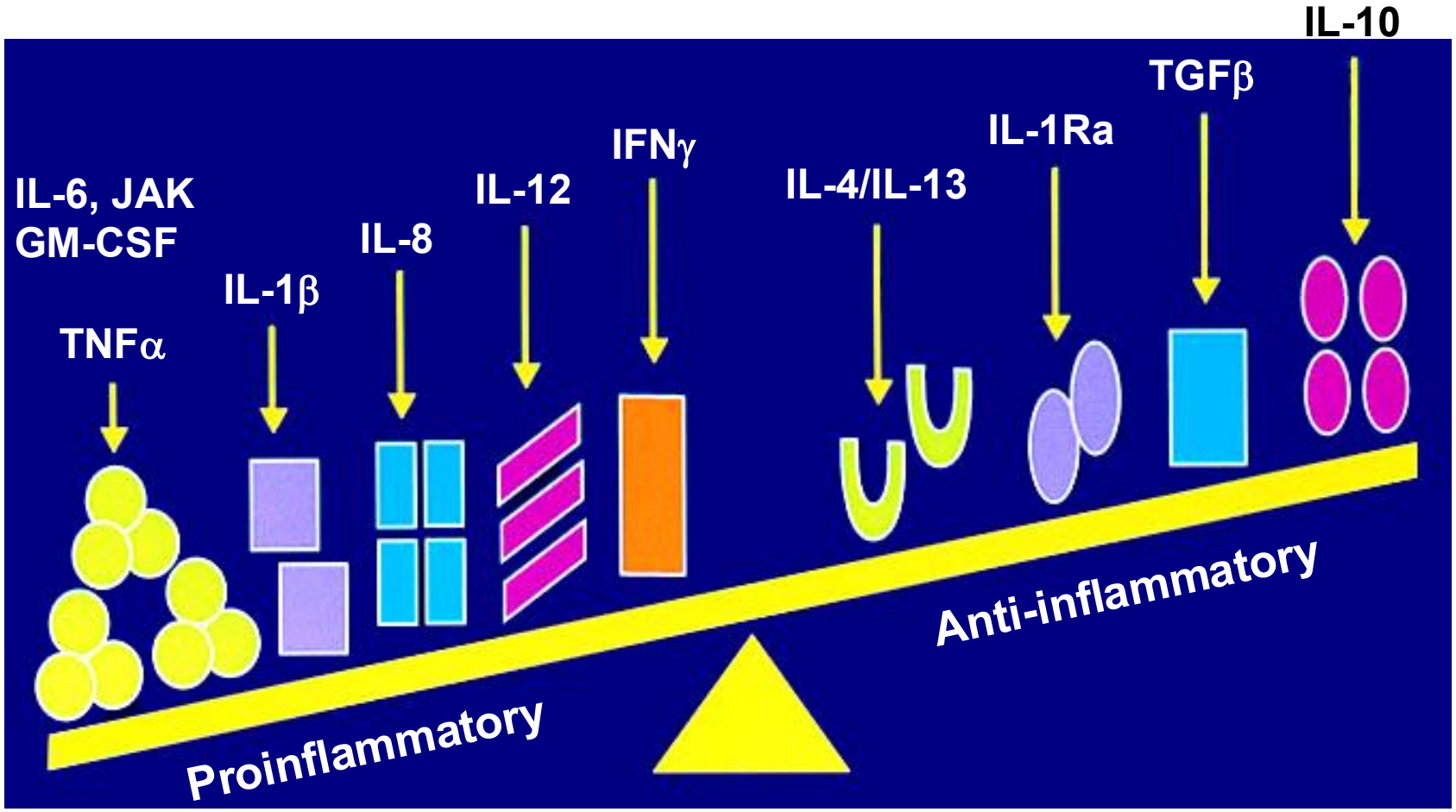
CHRONIC INFLAMMATION: IMBALANCE BETWEEN MEDIATORS



Mcinnes IB, Schett G. Nature Reviews. 2007;7:429-442.
Tracey D, et al. Pharmacology & Therapeutics. 2008;117:244-279.

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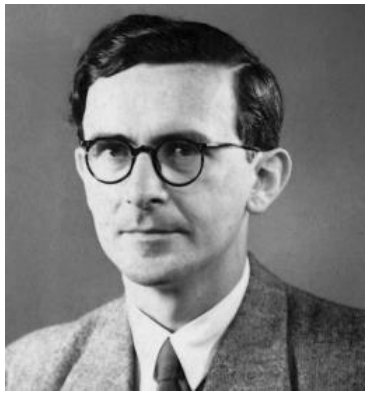
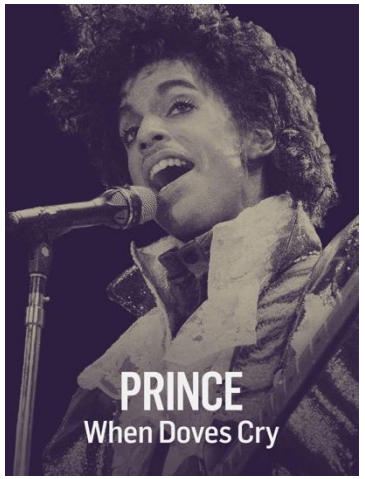
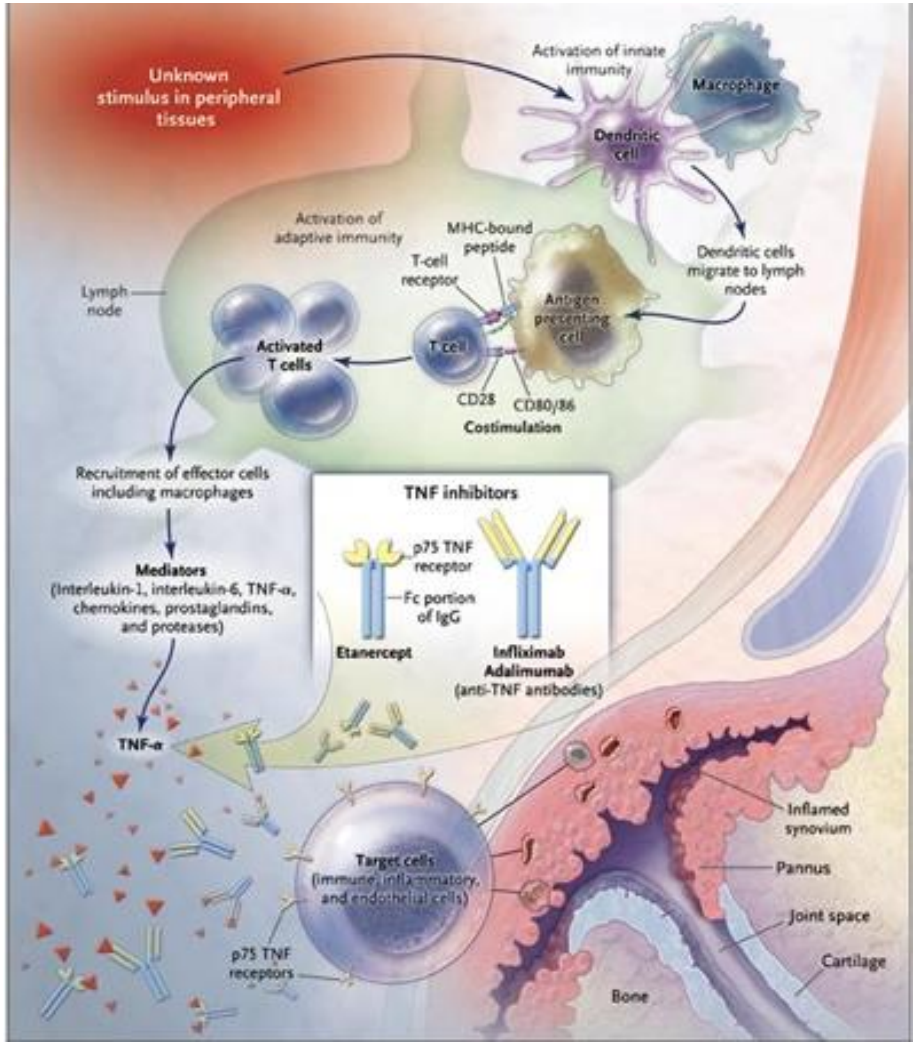
TUMOR NECROSIS FACTOR- α

- Hybridoma (Nobel, 1984) to produce mAb
  - Kohler, Milstein and Jerne





- Anti-TNF mAb
  - Maini and Feldmann
  - 1st 'targeted' therapy
  - Infliximab developed in 1992
  - FDA approval in 1998



Malaviya. A fascinating story of the discovery and development of biologicals for use in clinical medicine. Indian J Med Res 148, Sept 2018

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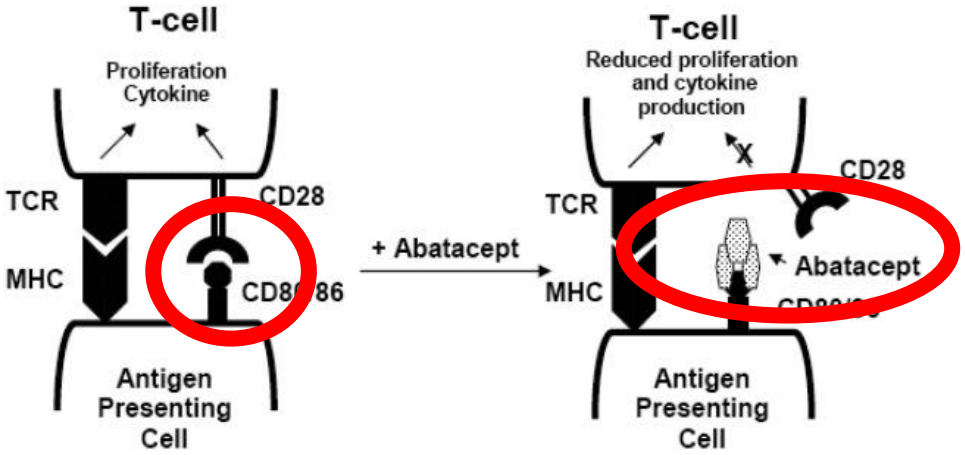
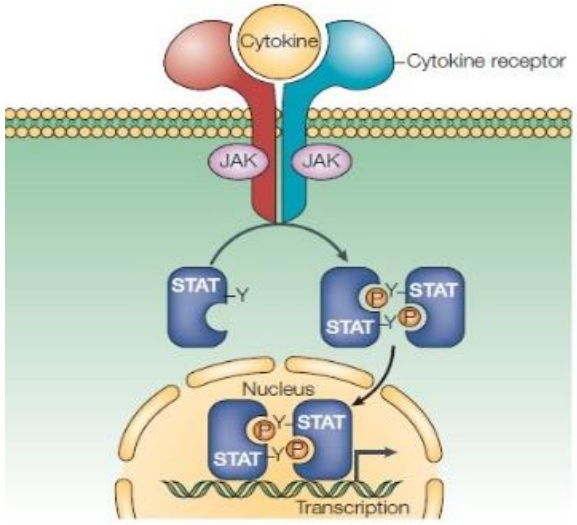
BIOLOGIC/TARGETED DMARD'S

- TNFα antagonists:
  - etanercept (Enbrel)
  - infliximab (Remicade)
  - adalimumab (Humira)
  - golimumab (Simponi)
  - certolizumab (Cimzia)
  - biosimilar infliximab, adalimumab
- Interleukin-1 antagonist
  - anakinra (Kineret)
- Suppress T-Cell activation
  - abatacept (Orencia)

- Anti B-Cell monoclonal Ab
  - rituximab (Rituxan)
  - biosimilar rituximab
- Anti-interleukin-6
  - tocilizumab (Actemra)
  - biosimilar tocilizumab
  - sarilumab (Kevzara)
- Janus kinase (JAK) inhibitors
  - tofacitinib (Xeljanz)
  - baricitinib (Olumiant)
  - upadacitinib (Rinvoq)





From Nature Reviews Immunology

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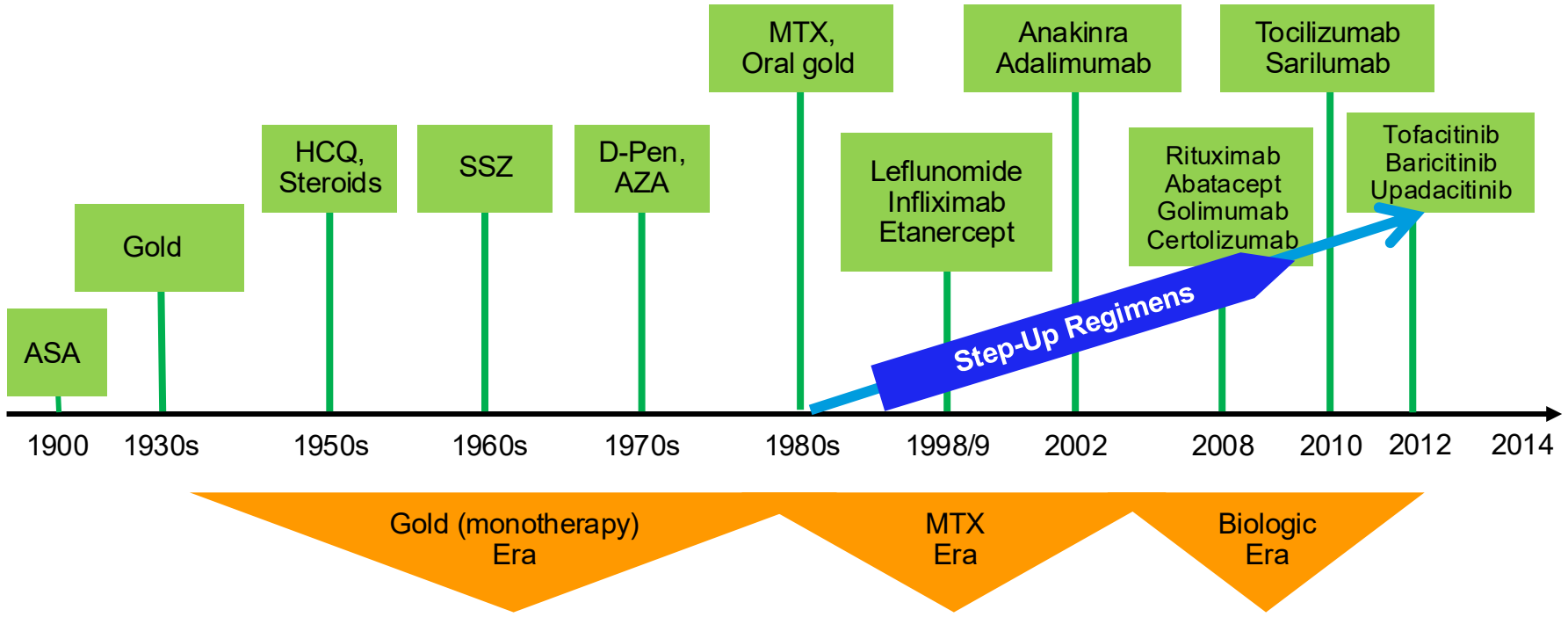
EVOLUTION OF RA TREATMENT



biosimilar$

- infliximab
- rituximab
- adalimumab
- tocilizumab

RA SUMMARY: INCORPORATING IMMUNOLOGY CONCEPTS

- Early diagnosis and classification criteria
- Immunopathogenesis (tobacco, gastrointestinal factors)
- Extra-articular domains, including ILD treatment guidelines
- Role of TNF and JAK in treatment

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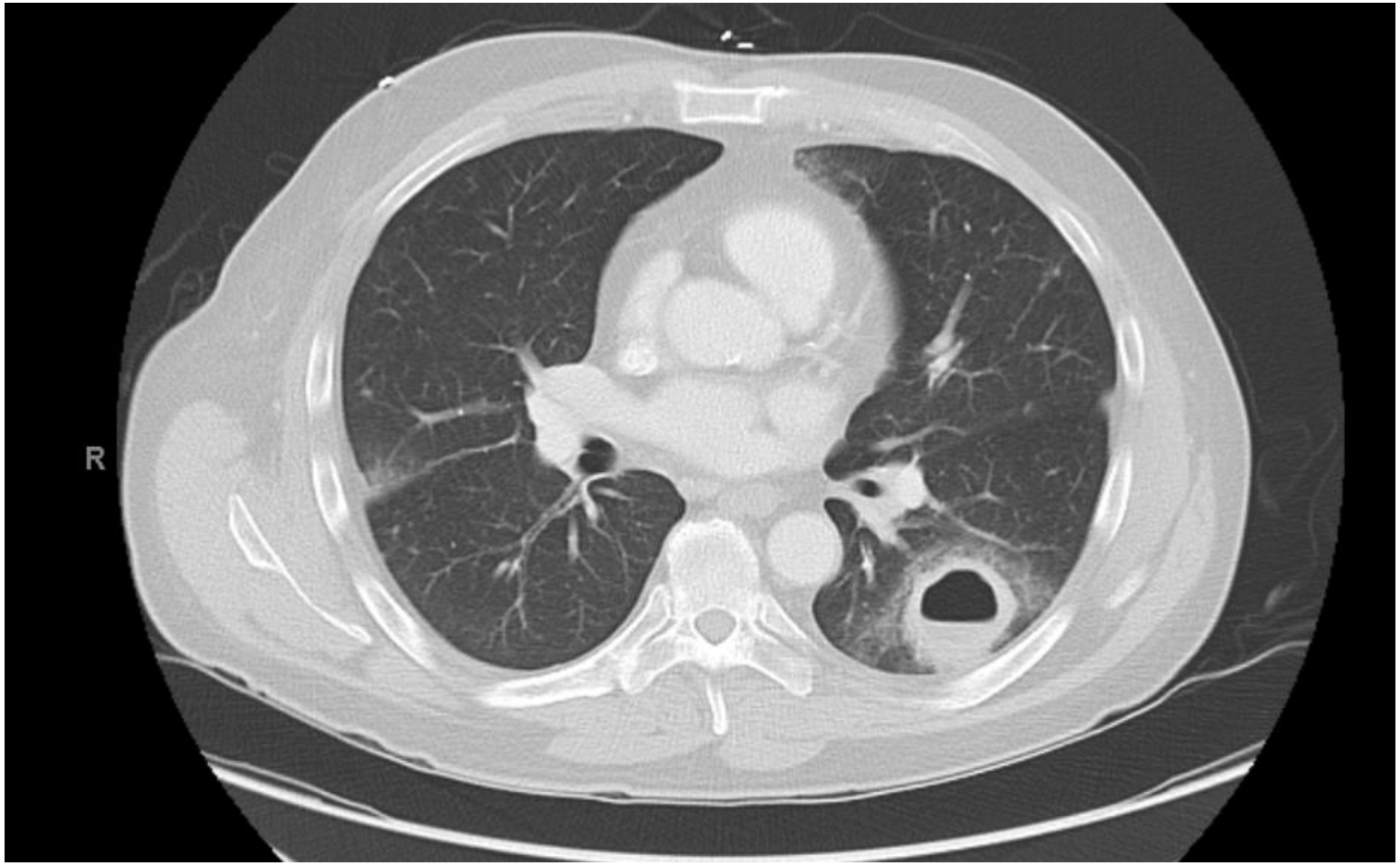
Case: 51 yo man admitted for 2 week history of fevers, night sweats, cough with hemoptysis, malaise. Moderate swelling and stiffness in hands and knees. Some eye redness and photophobia. Labs show AKI and high proteinuria. He works in agriculture in the central valley. No recent travel or ill contacts



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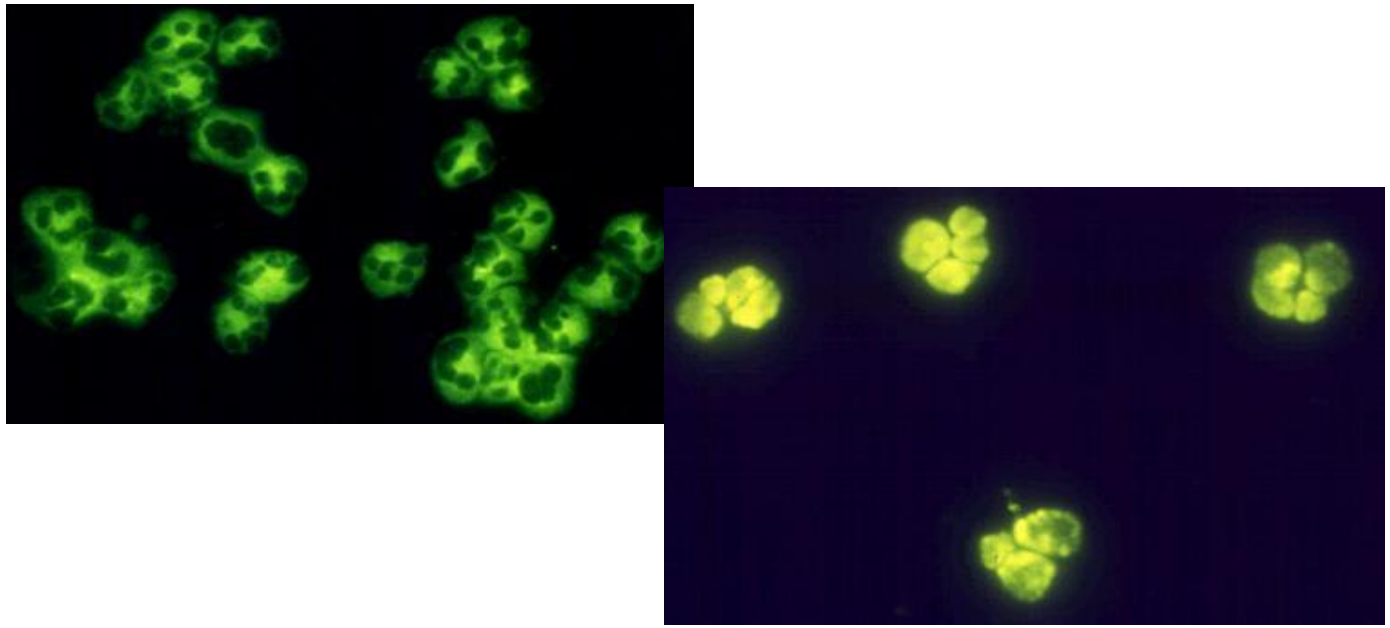
GRANULOMATOSUS WITH POLYANGIITIS/WEGENER'S

- Clinical presentation
  - Initially upper airway, sinus/ear manifestations
  - Refractory symptoms, pulmonary and renal usually follow
- Lab studies
  - C-ANCA, anti-proteinase-3 (microscopic polyangiitis (MPA) is P-ANCA, anti-myeloperoxidase)
  - ESR/CRP
  - anemia
  - renal
- Treatment
  - Corticosteroids
  - Cyclophosphamide (PO or IV)
  - Azathioprine, mycophenolate
  - Rituximab (April 11, 2011)
  - Avacopan (2021)



Carete, Vasculitis: What Have We Learned in the Last 50 Years? The Journal of Rheumatology 2022

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GRANULOMATOSUS WITH POLYANGIITIS/WG SOC

- Universally fatal…until:
- 1951 – glucocorticoids
- Thank you again, Dr Hench!

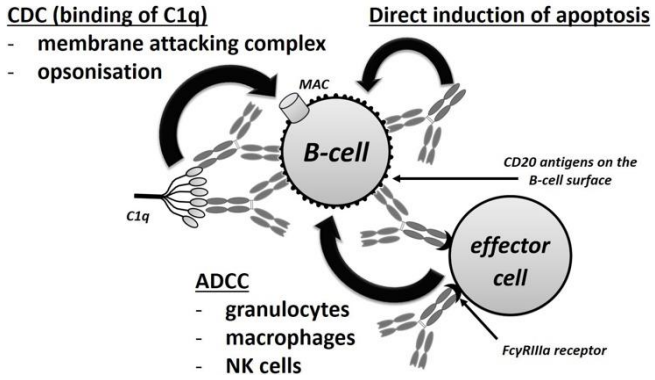
- 1970's – cyclophosphamide
- Anthony Fauci, NIAID

- 2011 – 1st FDA approved: rituximab
- RAVE trial

ORIGINAL ARTICLE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*



Stone. Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis N Engl J Med. Volume 363(3):221-232. 2010

Hartinger. Implications of rituximab pharmacokinetic and pharmacodynamic alterations in various immune-mediated glomerulopathies and potential anti-CD20 therapy alternatives. Front. Immunol., 06 November 2022

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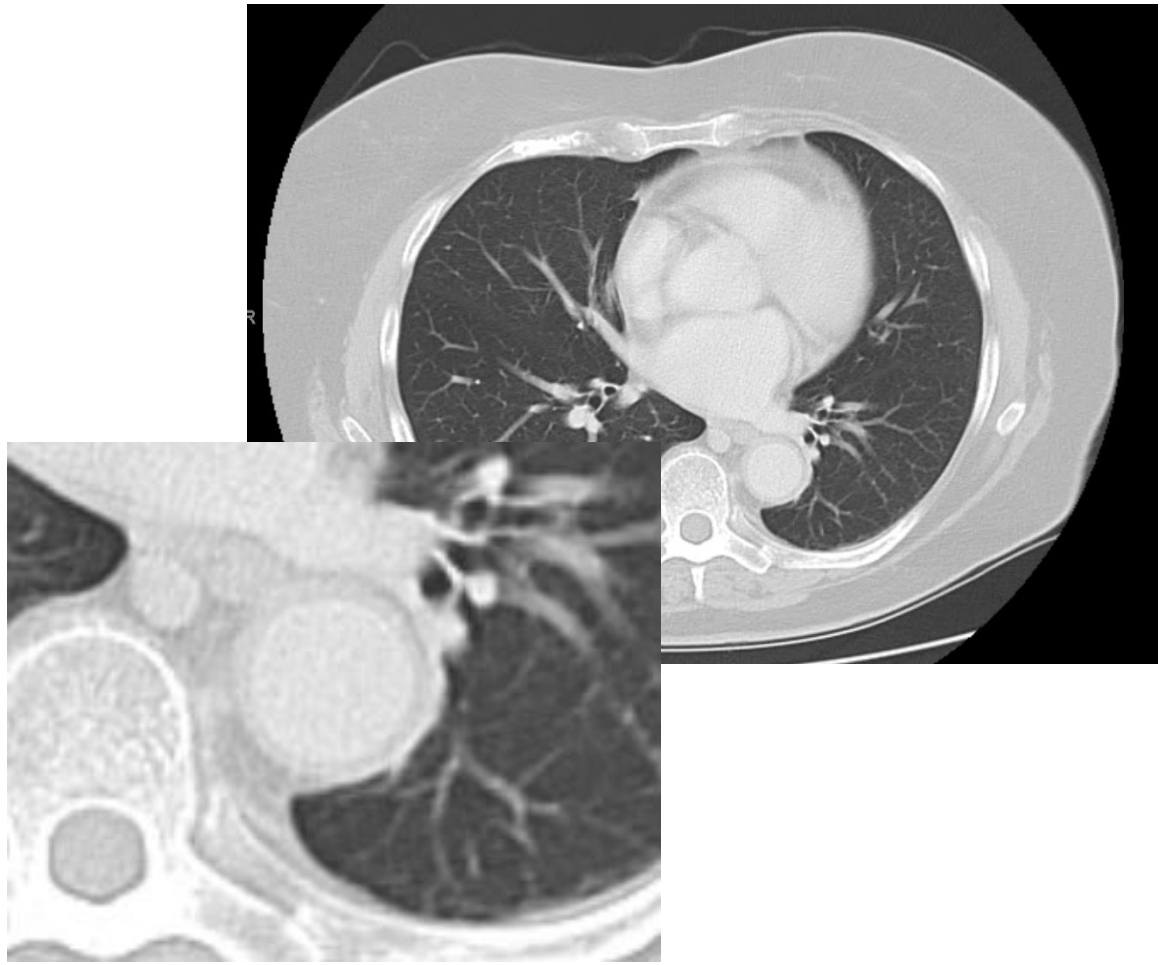
Q3: 82 year old WF with diabetes, osteoporosis (s/p vertebral compression fracture), chronic insomnia and cataracts presents to your office with a week of severe R sided headaches, fevers, malaise and new onset diplopia but no vision loss. Also 10 lbs weight loss over the past month. Body imaging is as shown. What is the next best step in management?

1. methotrexate
2. infliximab
3. leflunomide
4. methylprednisolone



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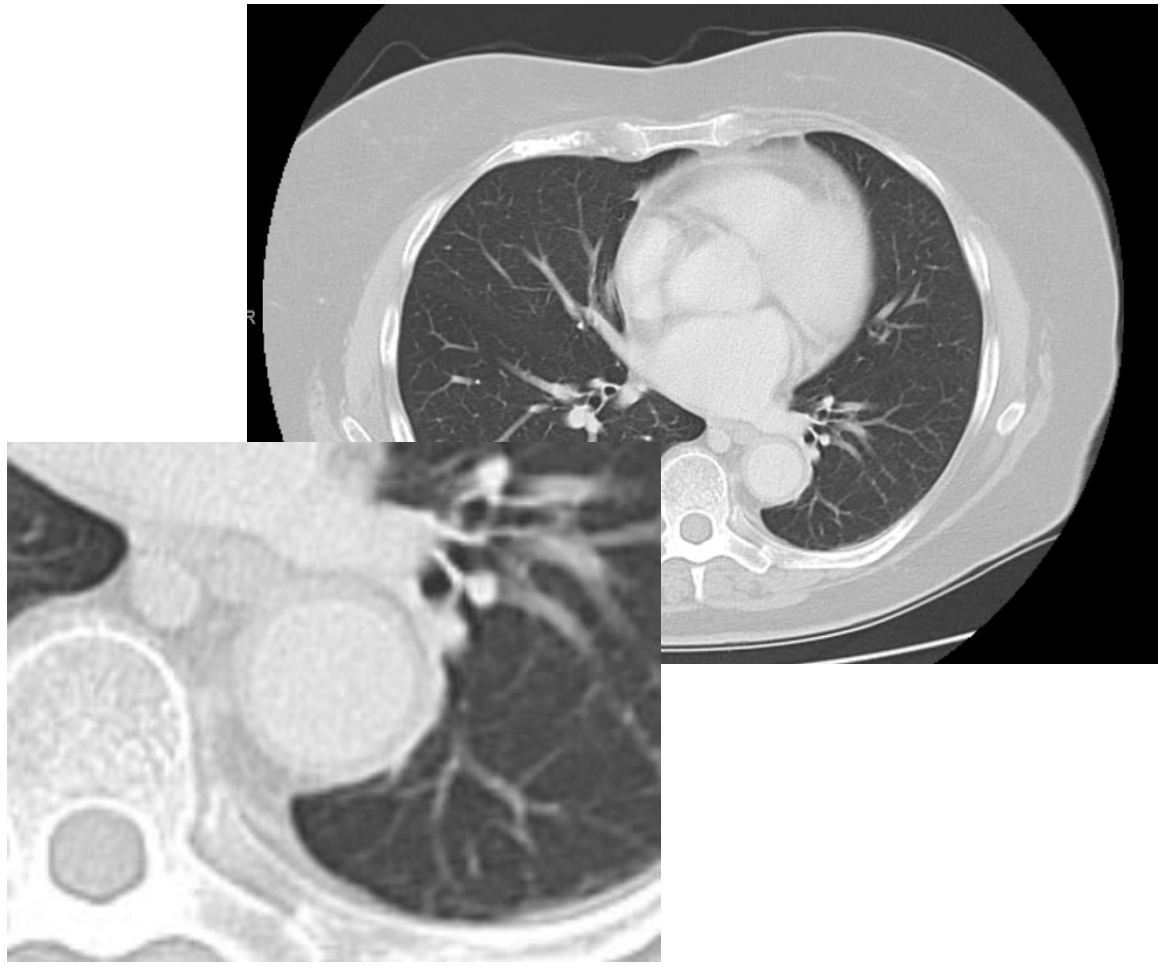

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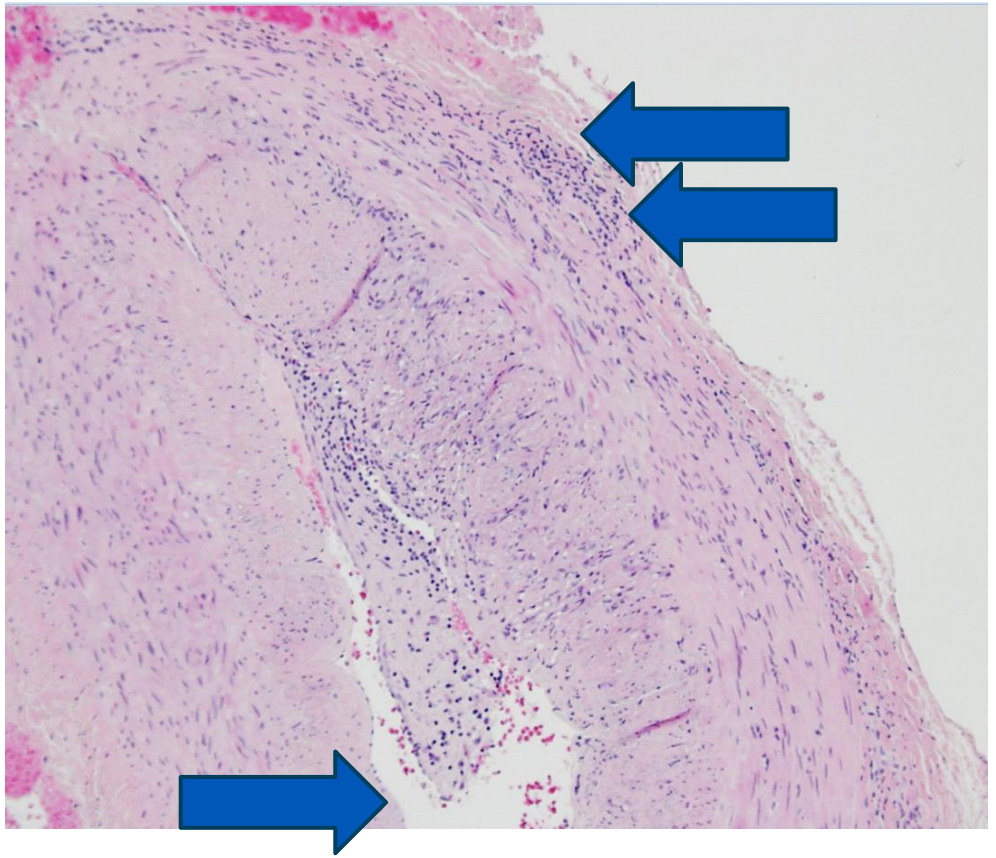
RATIONALE

- Giant cell arteritis requires prompt and urgent treatment to prevent vision loss
- Many anti-rheumatics have been studied but most have been disappointing
- Glucocorticoids have remained the mainstay
- Recent advances have added to the repertoire
- Imaging and biopsy add to diagnostic certainty



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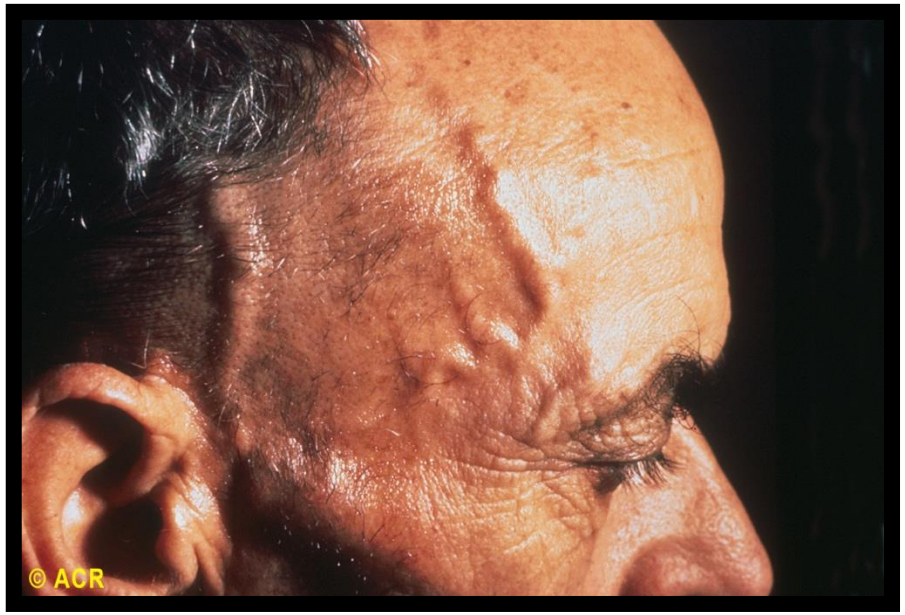

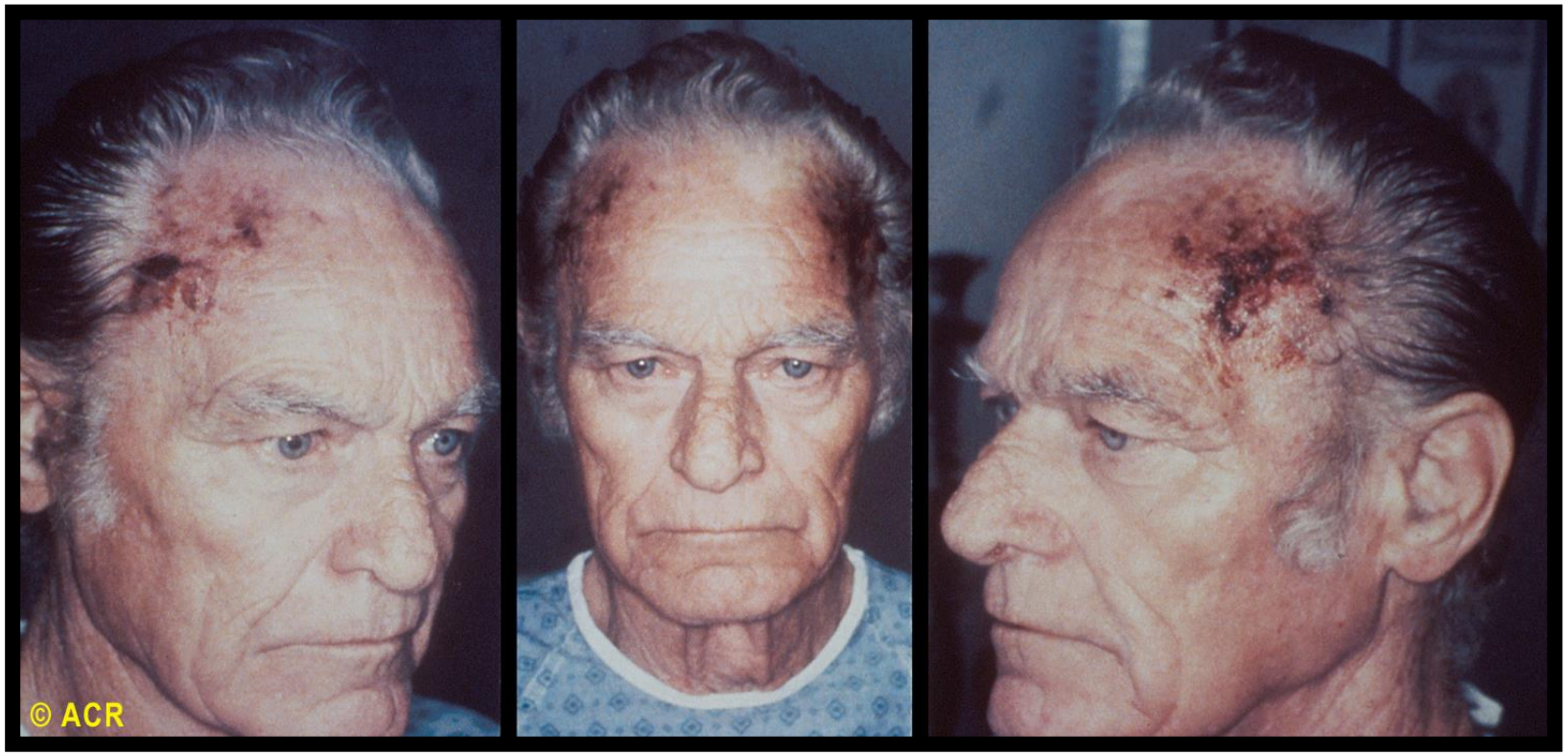

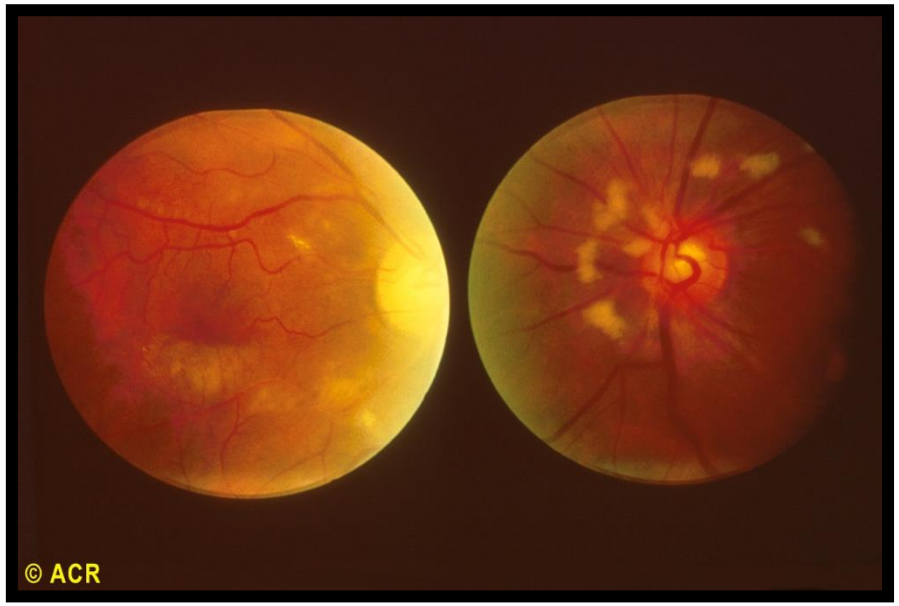

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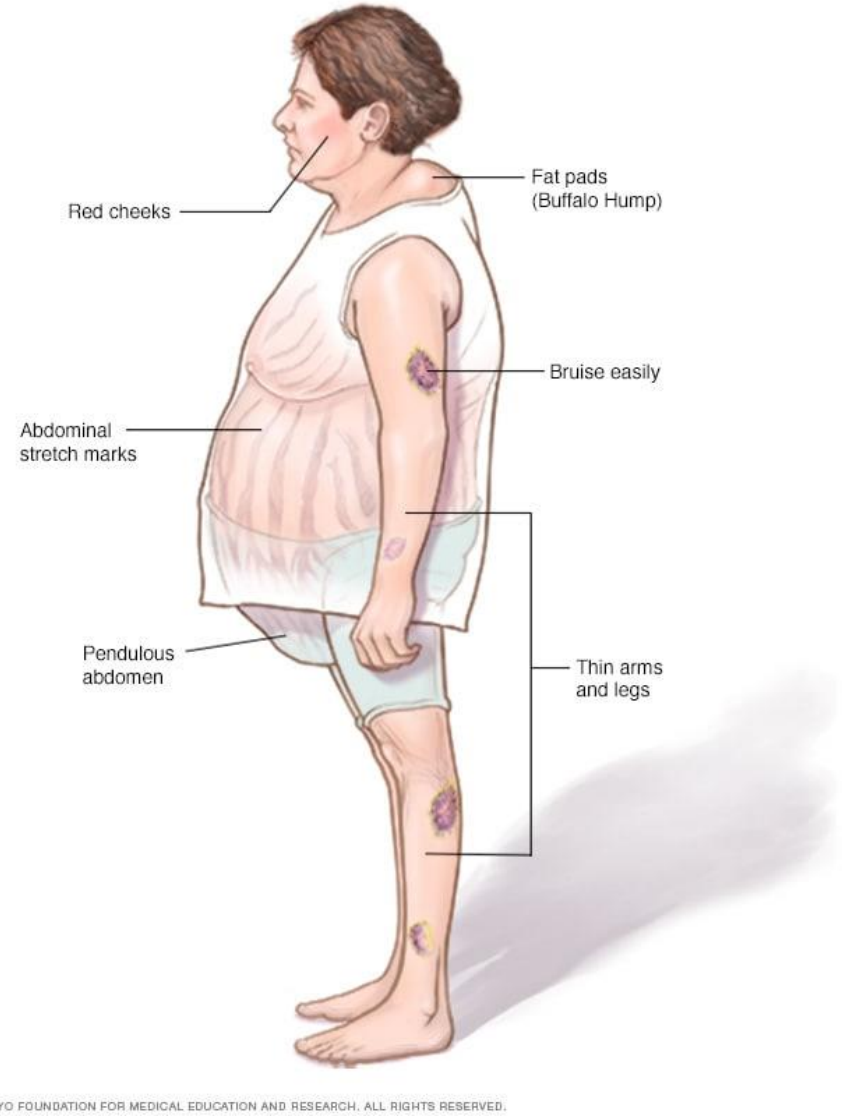
GCA – SOC (PRE-2017)

- Prednisone 1 mg/kg/day (60 mg) x 30 days, then taper
- IV methylprednisolone if severe (vision loss)

- Glucocorticoid induced osteoporosis (GIO)
  - Calcium with vit D
  - Bisphosphonates
  - Teriparatide



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https://www.mayoclinic.org/diseases-conditions/cushing-syndrome/symptoms-causes/syc-20351310

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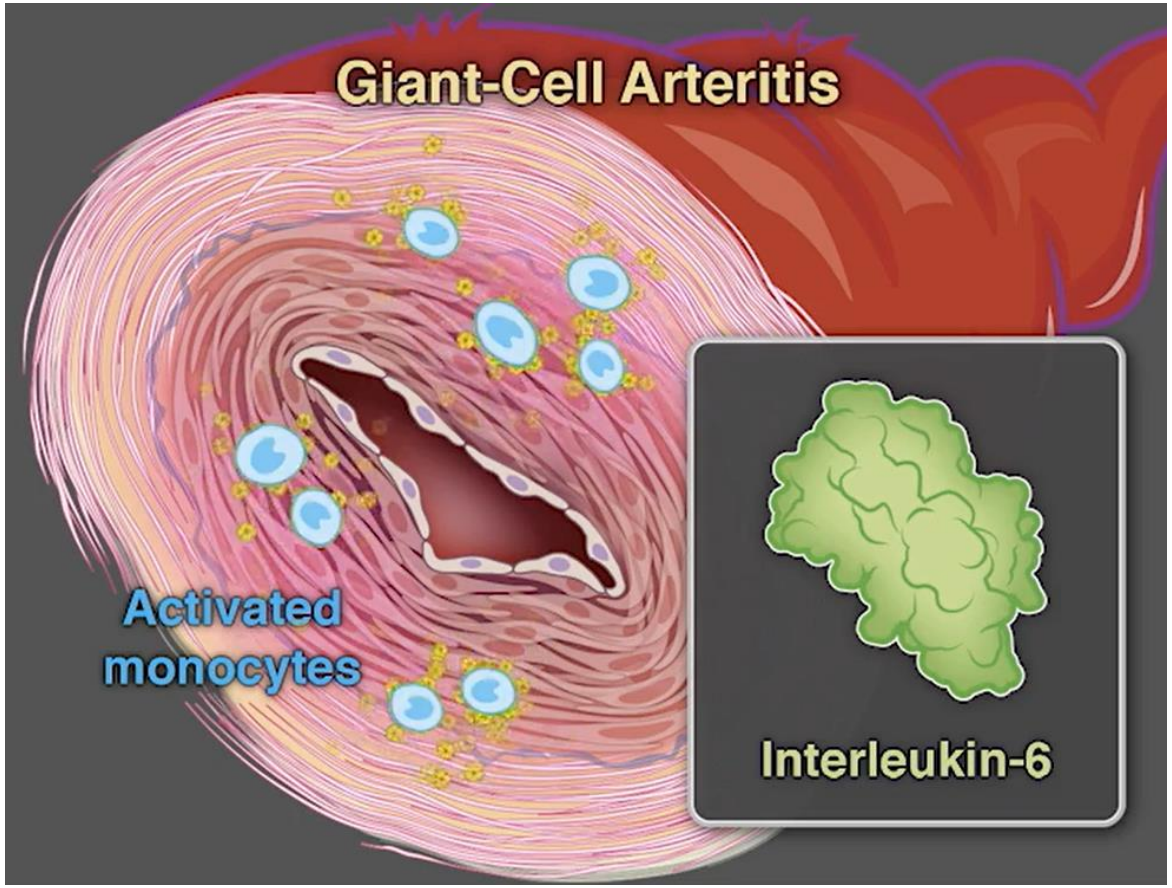
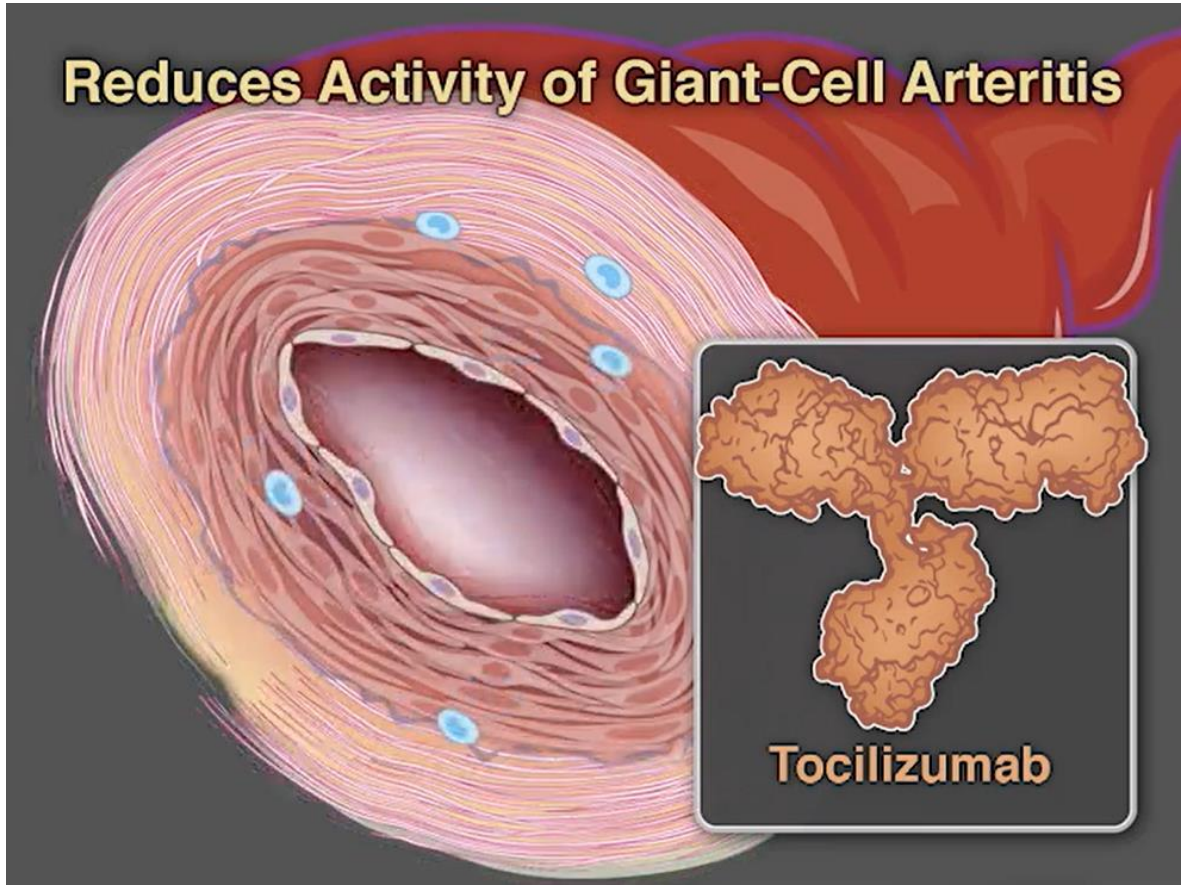
STONE, NEJM 2017





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Component	ESR	CRP
Latest Ref Rng & Units	0 - 30 mm/Hr	<=7.4 mg/L
10/31/2016	100 (H)	55.8 (H)
11/18/2016	71 (H)	18.5 (H)
1/13/2017	52 (H)	30.5 (H)
2/21/2017	51 (H)	28.2 (H)
3/10/2017	51 (H)	24.6 (H)
3/22/2017	68 (H)	59.3 (H)
5/4/2017	55 (H)	28.0 (H)
6/6/2017	43 (H)	24.9 (H)

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Component	ESR	CRP
Latest Ref Rng & Units	0 - 30 mm/Hr	<=7.4 mg/L
10/31/2016	100 (H)	55.8 (H)
11/18/2016	71 (H)	18.5 (H)
1/13/2017	52 (H)	30.5 (H)
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3/10/2017	51 (H)	24.6 (H)
3/22/2017	68 (H)	59.3 (H)
5/4/2017	55 (H)	28.0 (H)
6/6/2017	43 (H)	24.9 (H)
6/29/2017	9	<1.0
9/5/2017	5	<1.0
10/23/2017	4	<1.0
12/14/2017	5	<1.0
1/23/2018	4	<1.0

FDA approves first drug to specifically treat giant cell arteritis

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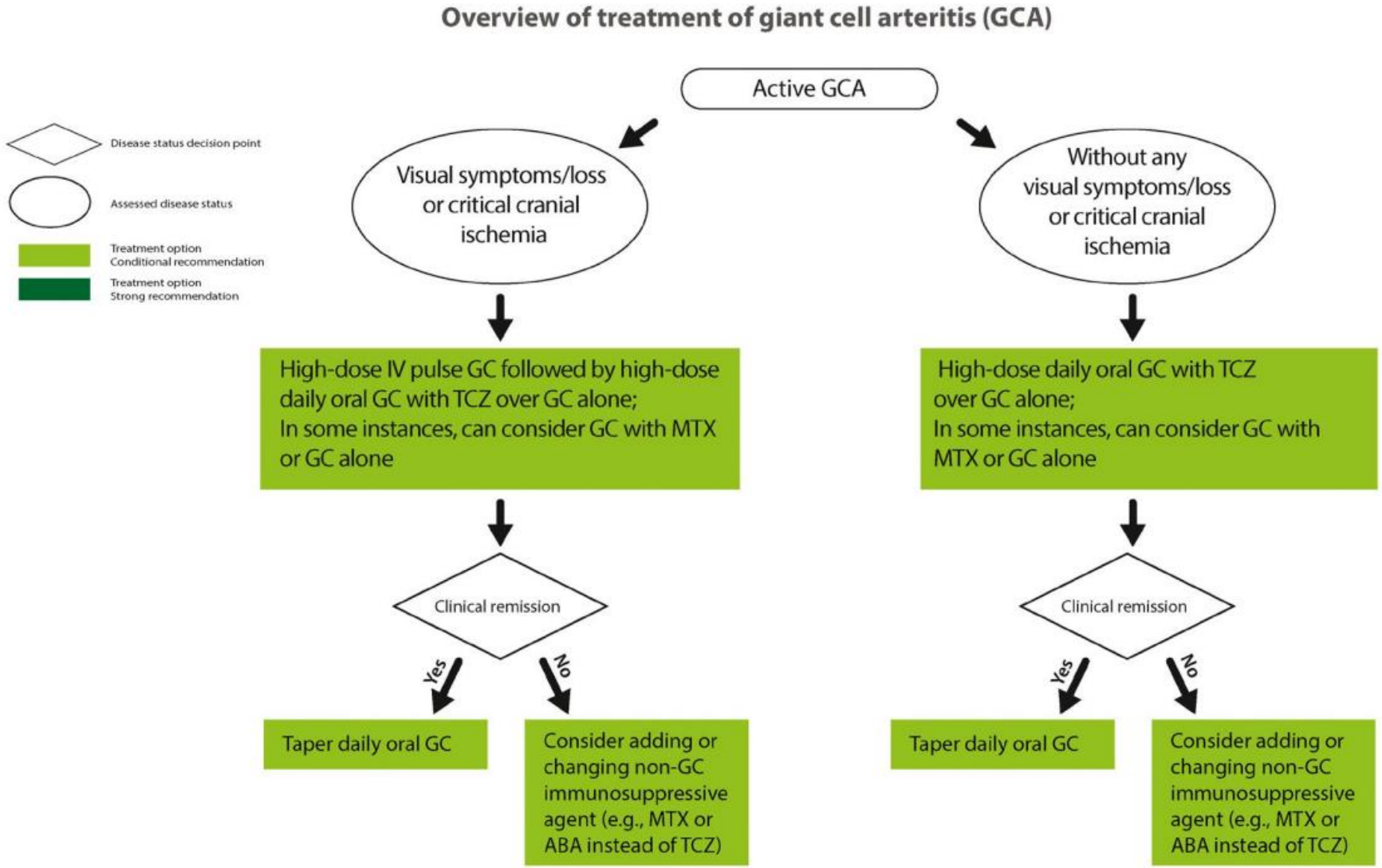
For Immediate Release

ESTABLISHED IN 1812 JULY 27, 2017 VOL. 377 NO. 4

Trial of Tocilizumab in Giant-Cell Arteritis

J.H. Stone, K. Tuckwell, S. Dimonaco, M. Klearman, M. Aringer, D. Blockmans, E. Brouwer, M.C. Cid, B. Dasgupta, J. Rech, C. Salvarani, G. Schett, H. Schulze-Koops, R. Spiera, S.H. Unizony, and N. Collinson

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis



ABA = abatacept, AZA = azathioprine, GC = glucocorticoids, IV = intravenous, MTX = methotrexate, TCZ = tocilizumab

Figure 1. Overview of treatment of giant cell arteritis.

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GCA 2025 UPDATE:

The NEW ENGLAND JOURNAL of MEDICINE

A Phase 3 Trial of Upadacitinib for Giant-Cell Arteritis

A Research Summary based on Blockmans D et al. | 10.1056/NEJMoa2413449 | Published on April 2, 2025

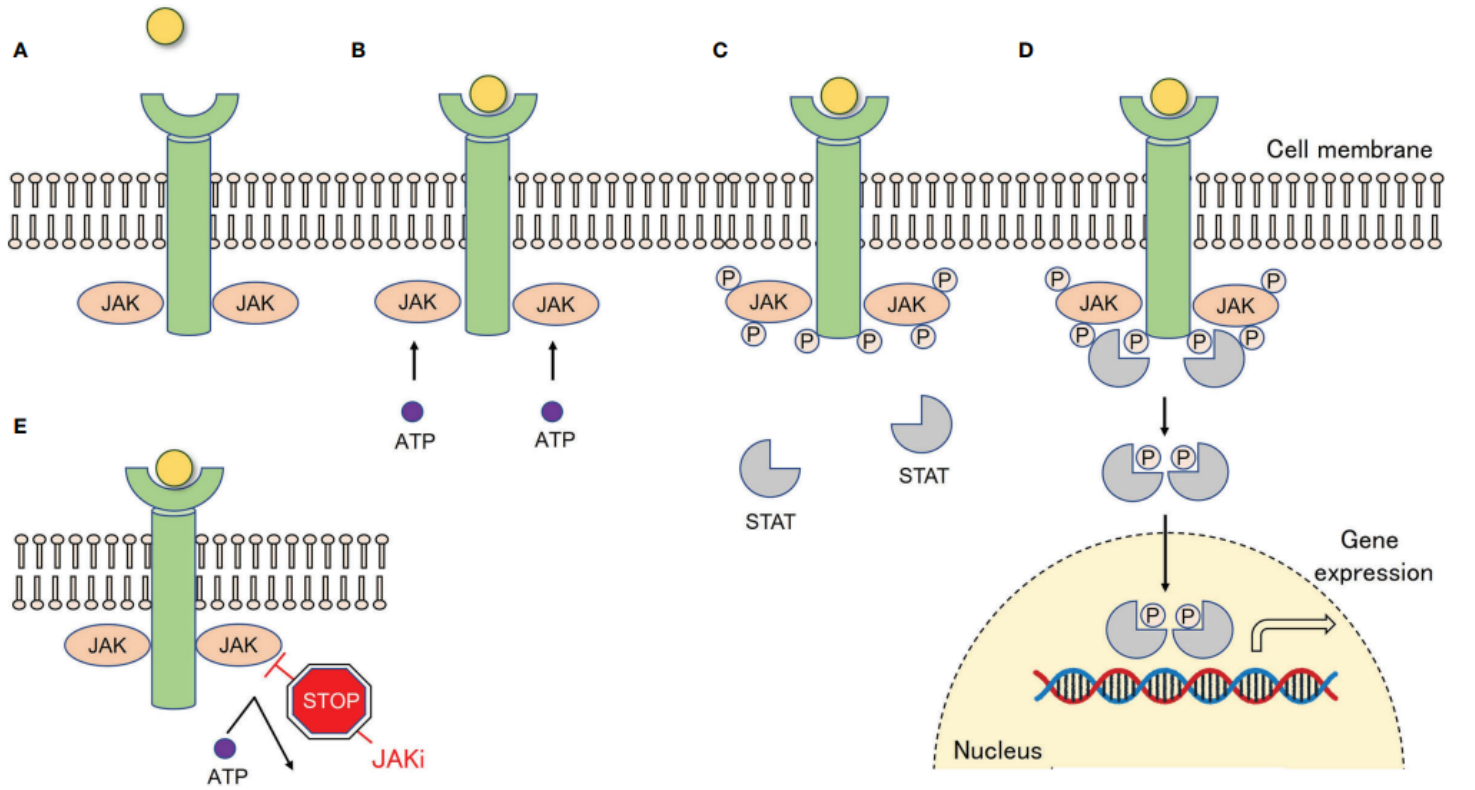

FIGURE 1 | The JAK-STAT pathway and mechanism of action of JAK inhibitors. **(A)** Type I and type II cytokines utilize the Janus kinase (JAK)-signal transducer and activation of transcription (STAT) pathway. **(B)** When type I and II cytokines bind to their receptors on the cell surface, JAKs bound to the intracellular domains are phosphorylated by adenosine triphosphate binding. **(C)** Phosphorylated JAKs, in turn, phosphorylate the receptor end. **(D)** The transcription factor STAT binds to the receptor end, and phosphorylated STATs form a dimer, which is then transferred to the nucleus to regulate gene expression. **(E)** JAK inhibitors competitively bind to the binding site of ATP, inhibiting phosphorylation of JAK and exerting their effects. ATP, Adenosine triphosphate; JAK, Janus kinase; JAKi, Janus kinase inhibitor; P, Phosphate; STAT, Signal transducer and activator of transcription.

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VASCULITIS SUMMARY: INCORPORATING IMMUNOLOGY CONCEPTS

- Early recognition remains key
- Immunopathogenesis (B cells in GPA, IL-6 and JAK in GCA)
- Glucocorticoids remain early mainstay
- Rituximab for GPA
- Tocilizumab and upadacitinib for GCA

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CONCLUSIONS

Importance of Immunology Knowledge

Understanding immunology enables doctors to better identify and treat rheumatic diseases in primary care

- Rheumatoid Arthritis
- Granulomatosus with polyangiitis (Wegener's)
- Giant Cell Arteritis (Temporal)

Effective Disease Management

Timely diagnosis and management improve patient outcomes and quality of life in rheumatic conditions.

Collaborative Healthcare Approach

Collaboration among healthcare professionals enhances treatment success and patient support.

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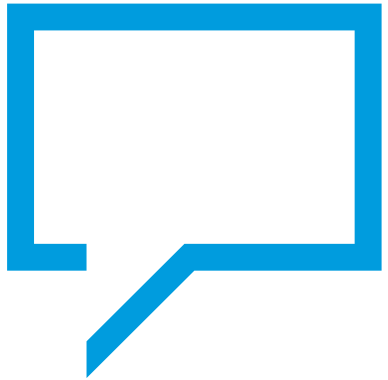
QUESTIONS & ANSWERS



STEVE.S1.LEE@KP.ORG

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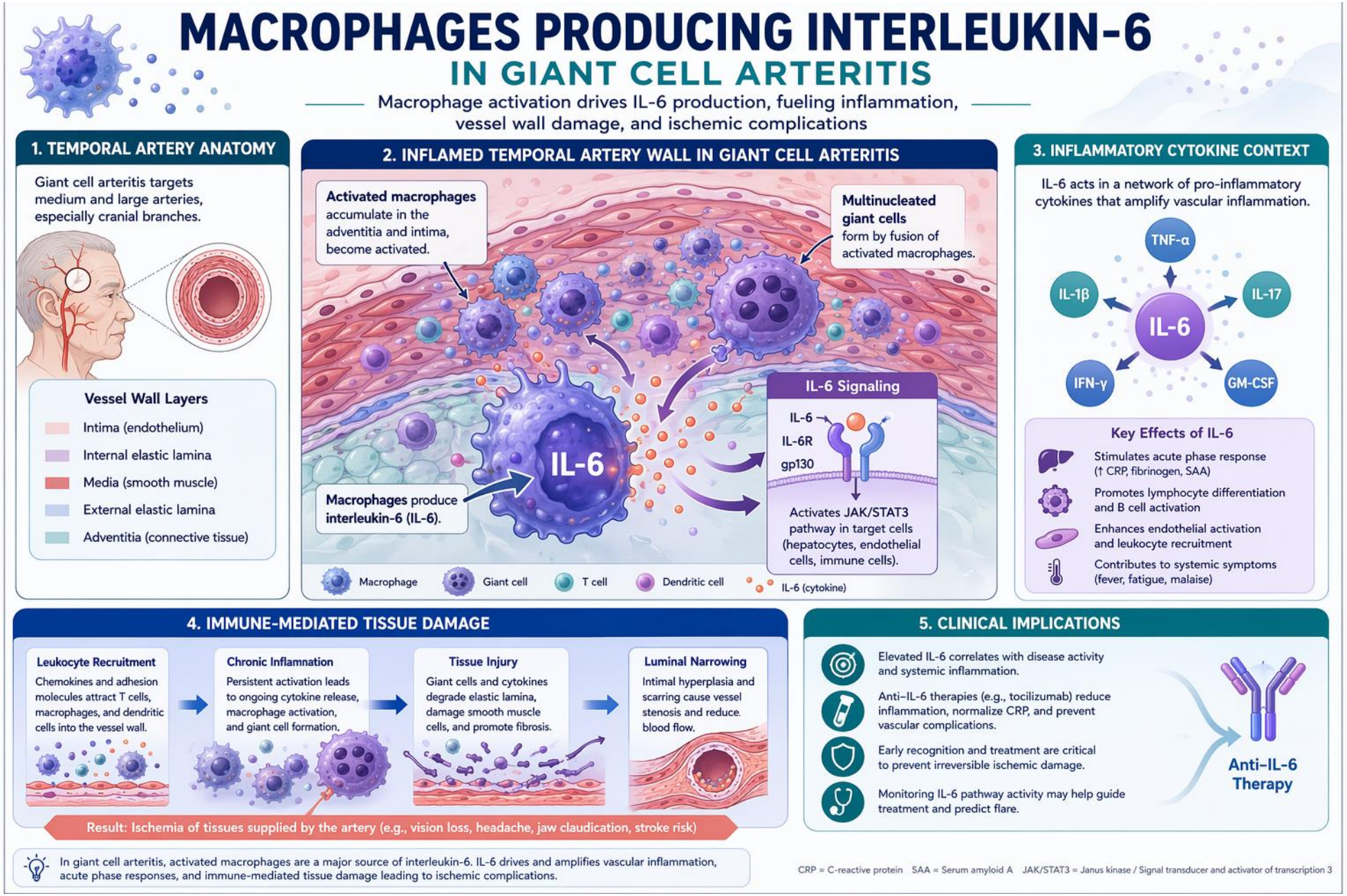

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