DMARD's – in Clinical Practice

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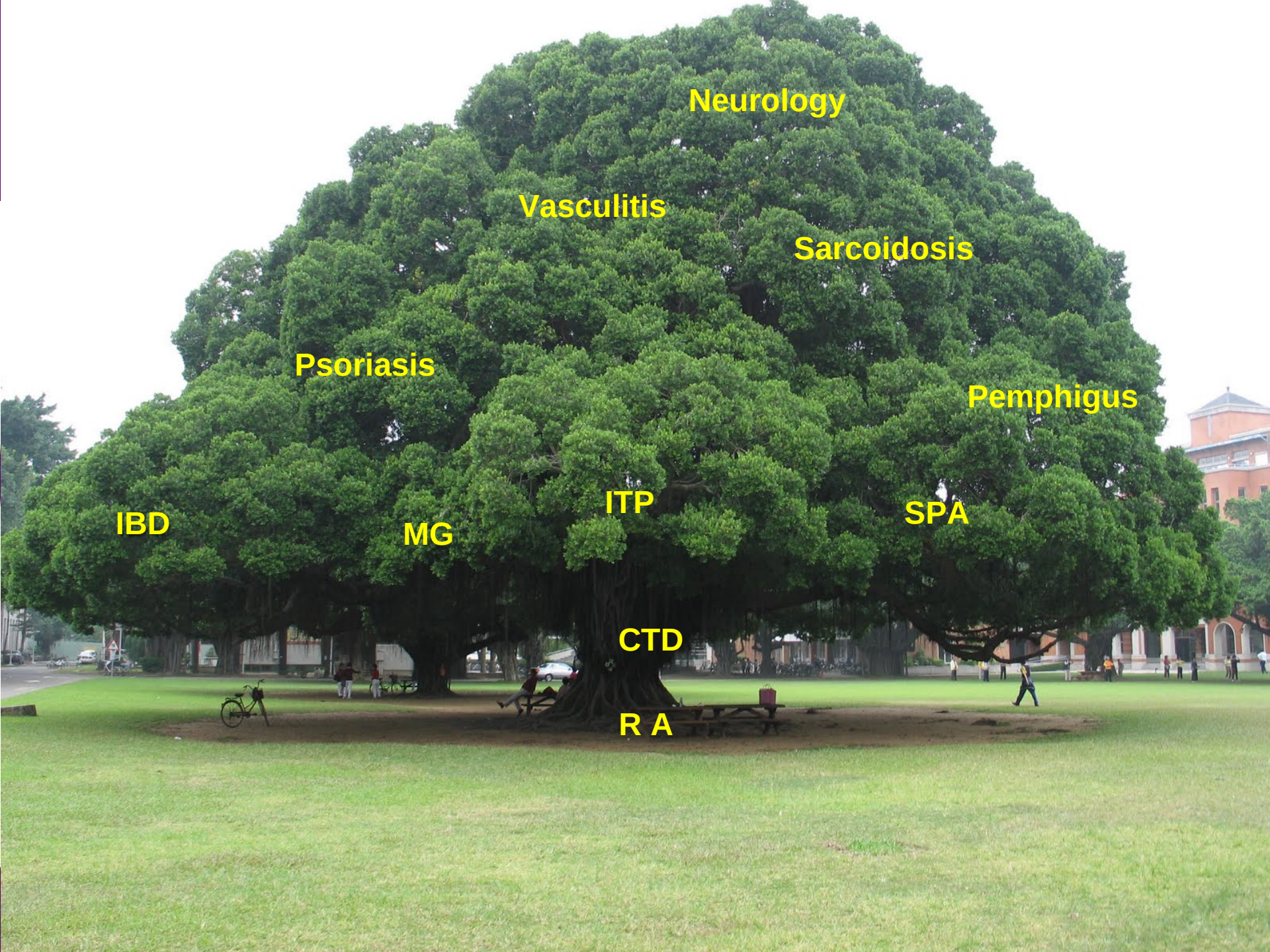
Disease-modifying antirheumatic drugs (DMARDs)

- A category of otherwise unrelated drugs defined by their use in rheumatoid arthritis to slow down disease progression.

- Disease modifying anti rheumatic drug- at Dorland's medical dictionary.


Neurology
Vasculitis
Sarcoidosis
Psoriasis
Pemphigus
IBD
MG
ITP
SPA
CTD
R A

What other fields for DMARD's

DMARD was first propagated in rheumatoid arthritis.

Later on.....

PSS	SLE	Inflammatory myositis	Vasculitis Myasthenia gravis Sarcoidosis	SPA, IBD, SLE, Sjögren's Syndrome ITP

DMARD's Categories

Systemic DMARDs

csDMARDs (conventional synthetic DMARDs): such as methotrexate or sulfasalazine

tsDMARDs (targeted synthetic DMARDs): tofacitinib, designed with specific molecular target.

Biological DMARDs

bo DMARDS (biological originator DMARDs): all original biological compounds

bsDMARDs (biosimilar DMARDs).

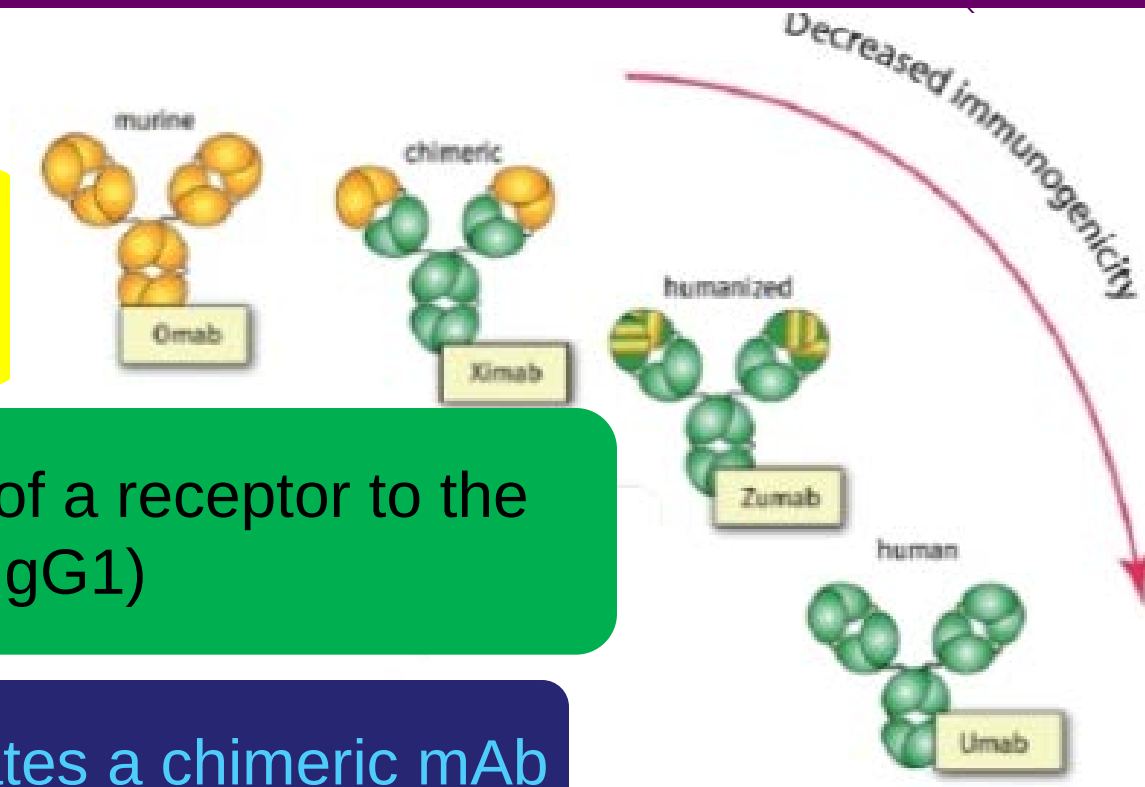
Contd....

- A biosimilar is defined by the WHO as a “biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

- World Health Organization. Expert Committee on Biological Standardization. Guidelines on evaluation of similar biotherapeutic products. Geneva, 2009.

http://www.who.int/biologicals/areas/biological_ (Accessed on September 28, 2013)

mab- indicates a monoclonal antibody (mAb)



cept- refers to fusion of a receptor to the Fc part of human (IgG1)

ximab- indicates a chimeric mAb

zumab- indicates a humanized mAb

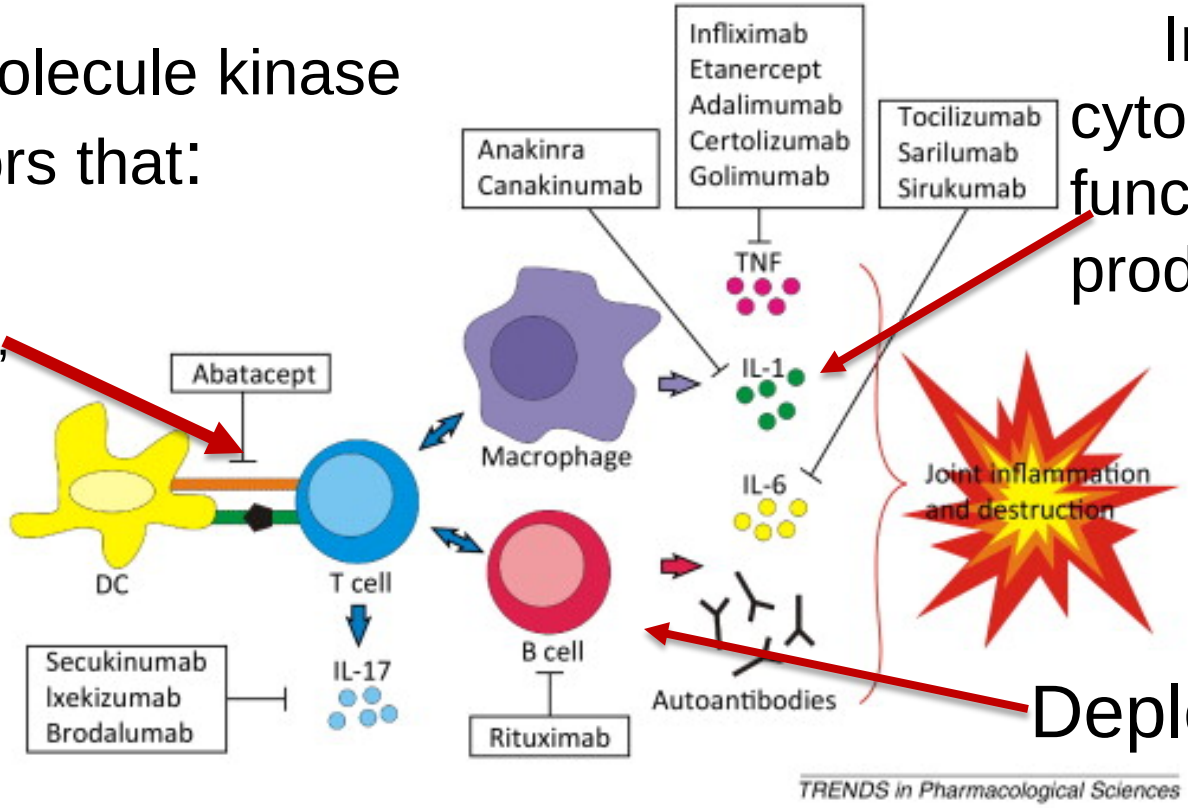
The major biologic approaches in clinical use

1. Medications made by molecular biologic techniques

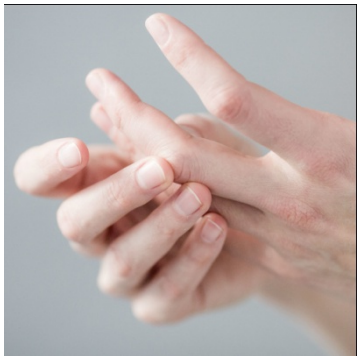
2. Small molecule kinase inhibitors that:

Inhibit the "second signal" required for T-cell activation

Interfere with cytokine function or production



Deplete B cells



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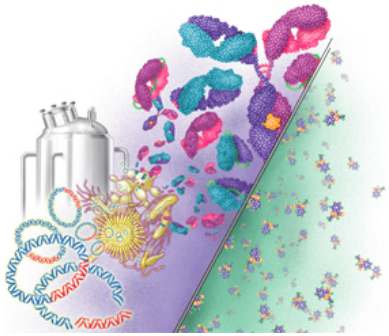
- DMARD's other than glucocorticoids are used to achieve one or more of the following goals:
  - To induce or maintain a remission
  - To reduce the frequency of flare or relapse
  - To allow tapering of glucocorticoids while maintaining disease control



Contd....

- They work to decrease pain and inflammation, to reduce or prevent joint damage, and to preserve the structure and function of the joints.

Contd....

- MTX typically serves as the “anchor” drug for the most commonly used DMARD combinations.

• Van Vollenhoven RF.Nat Rev Rheumatol. 2009;5(10):531.

Contd....

- In patients unable or unwilling to take MTX at the initiation of DMARD therapy - monotherapy with leflunomide, sulfasalazine hydroxychloroquine, TNF inhibitor (eg, etanercept or adalimumab), depending upon comorbidities, patient preferences, regulatory guidance, and disease severity.

• Up to date. Sep 13, 2016.

Contd....

- DMARD's available is of variable efficacy or may have serious adverse effects.

- Liu C, et al. Am J med.2012 May.125(3);292-301.

RELATIVE TOXICITIES

- No medication is without potential side effects.
- The risk to benefit ratio of any immunosuppressive drug varies with the experience of the clinician doing the monitoring, with the compliance of the patient, and with the presence of comorbid conditions.

Safety of DMARD's

- Safety of biologic and non-biologic DMARDs appears to be reasonable, particularly compared with the risks associated with the disease itself.
- Influenza and pneumococcal vaccine is recommended prior to Biologics use.
- Latent TB should be searched.

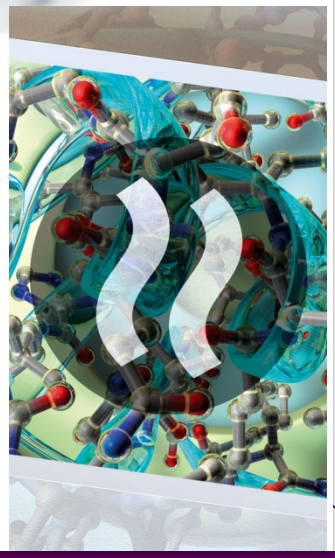
Eric M Ruderman.Rheumatology (2012) 51 (suppl 6): vi37-vi43. doi: 10.1093/rheumatology/kes283

MONITORING FOR TOXICITY

- The potential risks of adverse reactions can be minimized by regular clinical and laboratory assessment. Recommended monitoring depends upon the agent being used.
  - The results of reviews are not dissimilar with available DMARDS.
  - Studied showed broadly equivalent effects.

Arthritis Rheum 1996; 39:723.

Important precautions before using DMARDs



- CBC
- Serum creatinine,
- Aminotransferases, and other studies as indicated, evaluation of comorbidities, vaccinations, and screening for HCV, HBV and latent tuberculosis infection-CXR
- MTX hypersensitivity pneumonitis in patients with underlying pulmonary disease, and having a baseline chest radiograph

In RA

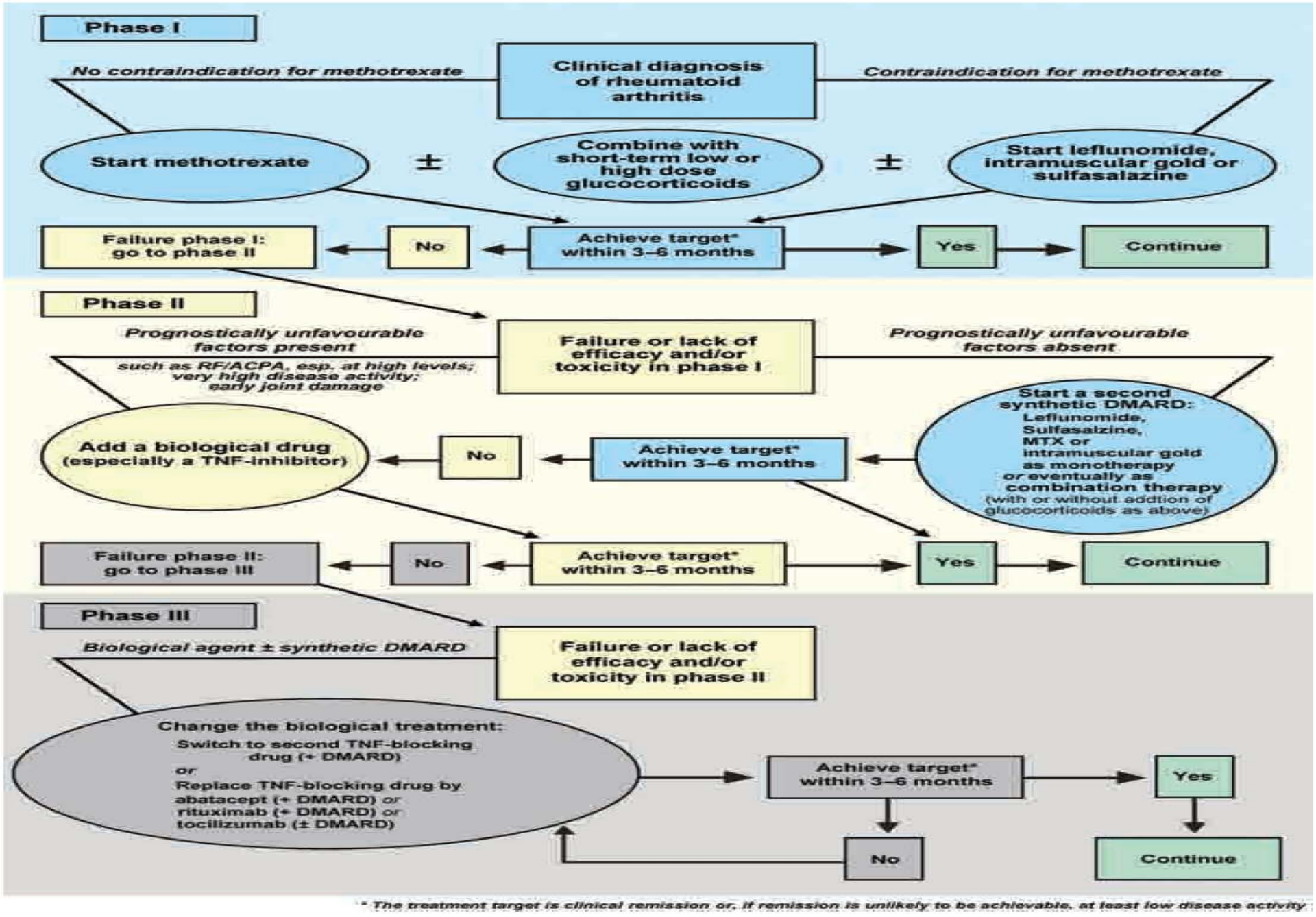
- Disease-modifying antirheumatic drugs (DMARDs) should be used early and aggressively at the first sign of rheumatoid arthritis (RA)
- 11-year trial, published in BioMed Central's open access journal Arthritis Research & Therapy.

- News Medical life Sciences. June 24, 2010.

Contd....

- Look for- Prognostic markers - predicting a poor prognosis in RA-
- High RF, ACPA
- Functional limitation
- Extraarticular disease
- Bony erosions documented radiographically

• Kloppenburg M et al.Arthritis Rheum. 1994;37(5):629.



EULAR recommendations on RA

Ann Rheum Dis 2010;69:964–975.
doi: 10.1136/ard.2009.126532

Contd....

- MTX as DMARD of choice for initial treatment of patients with active RA.
- MTX serves as “anchor” drug for most commonly used DMARD combinations.

- American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guideline. Arthritis Rheum. 2002;46(2):328.
- Maetzel A et al.J Rheumatol. 1998;25(12):2331.

Contd....

Patients diagnosed with active RA should receive DMARDs to prevent, arrest, or retard disease-related injury. Recommendations of major groups support the early use of DMARDs, usually MTX.

- Smolen JS, et al.Ann Rheum Dis. 2010;69(6):964.
- Smolen JS, et al.Ann Rheum Dis. 2014;73(3):492.

Contd....

- Severely active RA; those with an inadequate response can be quickly identified and subsequently treated with combination therapy prior to the development of irreversible injury.

- Breedveld FC, et al. Arthritis Rheum. 2006;54(1):26.
- Emery P, et al.Arthritis Rheum. 2010;62(3):674.

Contd....

- MTX is contraindicated in several groups of patients. These include:
- Women- contemplating becoming pregnant
- Women who are pregnant
- Liver disease or excessive alcohol intake
- Patients with severe renal dysfunction- eGFR<30 mL/min.

Contd....

- Other potent DMARDs that can be effective as initial monotherapy include tocilizumab, which is administered by subcutaneous injection or intravenous infusion, and tofacitinib, the orally administered Janus kinase (JAK) inhibitor.

Contd....

- Initial remission targeted therapy with DMARD combination in early RA is safe for Kidney and does not induce more short or long term renal complications compared to traditional therapy with a single DMARD.

• Clinical and Experimental Rheumatology 2010;28:73-78.

MONITORING AND REEVALUATION

- During the initial treatment of patients with active rheumatoid arthritis (RA), the patient should be reevaluated every four to eight weeks, depending upon several variables.

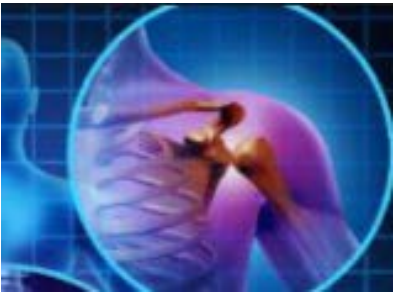
- American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines.Arthritis Rheum. 2002;46(2):328.

Autoimmune disease

- Although most of the FDA approved Biologic therapy are for RA.
- Belimumab is the 1st approved for SLE.
- In addition, the efficacy and safety of biological in off level indications are encouraging for patients with resistant autoimmune disorders.

- Rosman et al. BMC Medicine 2013,11:88.

In SPA



- Sulphasalazine and MTX are traditional DMARD's for AS and other SPA.
- TNF antagonist can be used.
- Other biological still on trial and controversies.

• Keith et al. Rheumatol Curr Res. 2013,3:2.1000119

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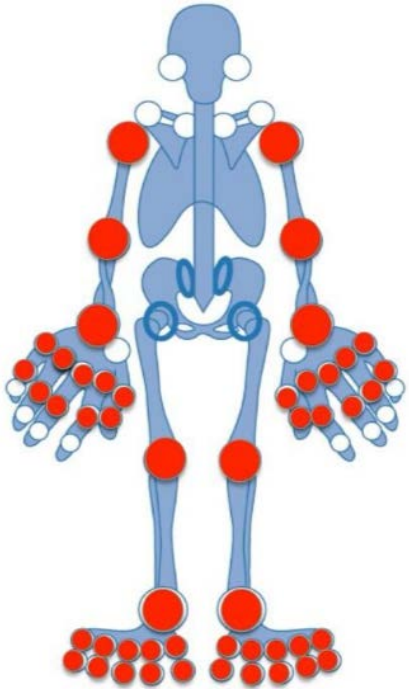
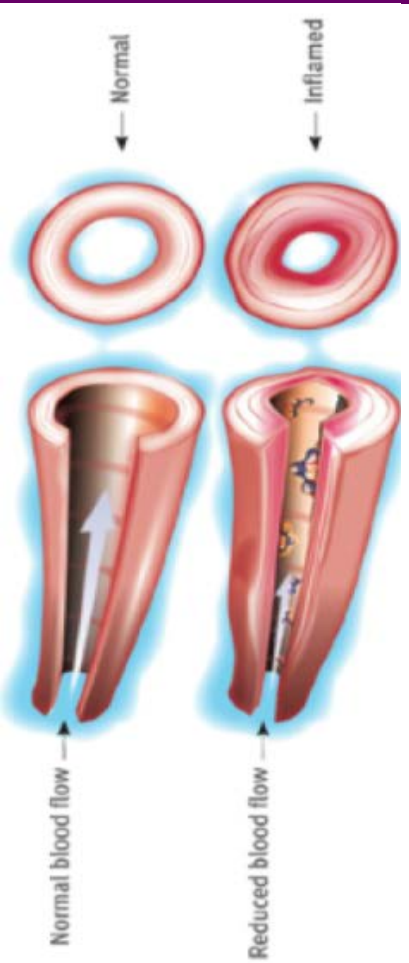


- Concomitant use of MTX may improve drug survival, reduce immunogenicity and prevent secondary inefficacy, which is of particular significance in AS and psoriatic arthritis.

- Medscape. December 3,2016.

In Vasculitis



- Remission induction and maintainence of vasculitis- use of medium to high doses of glucocorticoids, with the use of an additional DMARD's in some forms of disease.

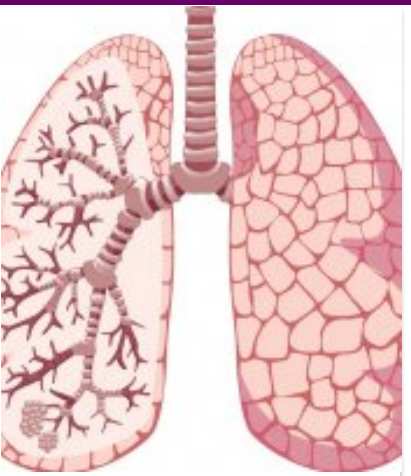
Up to date. 14 October 2015.

In Sarcoidosis

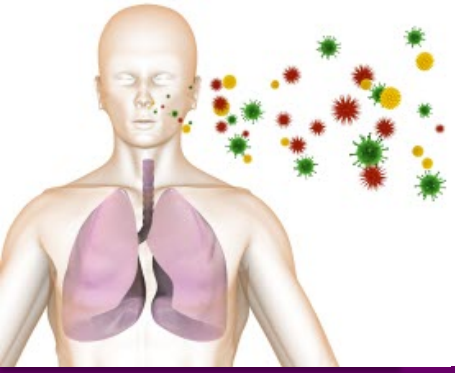
- DMARD's- especially Biologics, have been shown to improve index organ involvement in patients with refractory sarcoidosis.
- Response rate to methotrexate of 40 to 60% among patients with pulmonary sarcoidosis.

- Semin Respir Crit Care Med. 2010;31(4):463-473.
- Agrawal S, et al. Sarcoid sacroiliitis: successful treatment with infliximab. Ann Rheum Dis 2009;68:283
- Santos E, et al.Treatment of refractory neurosarcoidosis with infliximab. J Neurol Neurosurg Psychiatry 2010;81:241–246
- Baugman RP, et al.Clin Chest Med. 2008;29(3):533.

In ILD

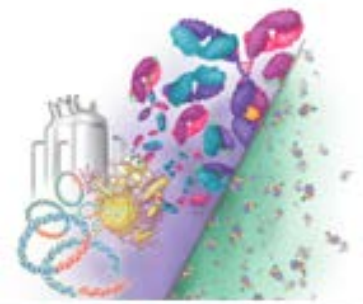


- Interstitial lung disease that has a known inflammatory or autoimmune process may benefit from initial anti-inflammatory or immunosuppressing medications, DMARD's.



http://www.mayoclinic.org/diseases-conditions/interstitial-lung-disease/basics/treatment/con-20024481

In ITP



- Second-line therapy for ITP symptoms, severe, persistent or recurrent thrombocytopenia platelet count <20,000/microL following glucocorticoid.
- For second-line therapies, recommendation- splenectomy or Rituximab rather than chronic glucocorticoids.

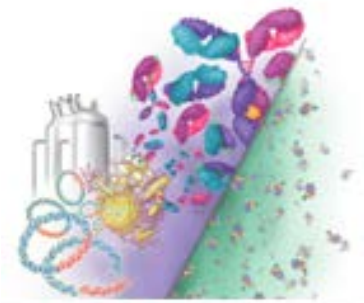
Up to Date.Nov 15, 2016.

Mutiple sclerosis-Neurology

- Have important beneficial effects for patients with relapsing-remitting multiple sclerosis (RRMS):
- A decreased relapse rate.
- A slower accumulation of brain lesions on MRI.

• Tramacere I, et al. Cochrane Database Syst Rev. 2015;

In IBD



- Crohn's disease (CD) and ulcerative colitis (UC) that are being treated with commonly prescribed DMARD medications; thiopurines, aminosalicylates, methotrexate and ciclosporin.

Contd....

- A recent study reported that use of biologics (especially TNFα inhibitors) in the early stages of CD leads to less use of corticosteroids and also CD related surgeries in the later stages of disease.

• D T Rubin, et al. Inflamm Bowel Dis, Volume 18, 2012, pp. 2225–2231

Contd....

- Non-biologic and biologic, both DMARD's are in use increasingly for Inflammatory bowel disease.

William J, et al.Gastroenterology & Hepatology.Volume 12, Issue 7, July 2016.

In Dermatogy

- In pemphigus and pemphigoid- DMARD's both synthetic and biological.
- Rituximab and intravenous immunoglobulin may be helpful in particularly severe Dermatitis herpetiformis. Less effective include cyclosporine, azathioprine.

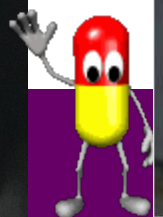
- @healourskin-29 November,2016.
- J Am Acad Dermatol. 1992Aug.27(2Pt 1);209-213.

Contd....

- MTX used successfully in psoriasis for over 30 years.
- Biologic agents are important treatment options for moderate to severe plaque type psoriasis.
- The available biologics for psoriasis have excellent short-term and long-term efficacy and favorable tolerability.
- Biologic therapies include etanercept, Secukimumab, infliximab, adalimumab, ustekinumab, secukinumab, and ixekizumab.

- Gottlieb SL.Nat Med. 1995;1(5):442.
- Fallen JP,. J Am Acad Dermatol. 2003;49(2):351.
- Boehnche. WH Et al,,J Rheumatol. 2006;33(7):1447.

Key Messages

- In clinical use, DMARD's have role in RA and other Rheumatological diseases, autoimmune disorders.
- Not confined in only Rheumatology- this drugs are now used in many other systemic diseases.
- Overall, the safety of biologic and non-biologic DMARDs appears to be reasonable.
- Safety precaution and monitoring is required in using both nonbiological and biologic DMARD's.

THANKS