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Infusion/In-Office TNFa-Inhibitors for Adults with Rheumatoid Arthritis

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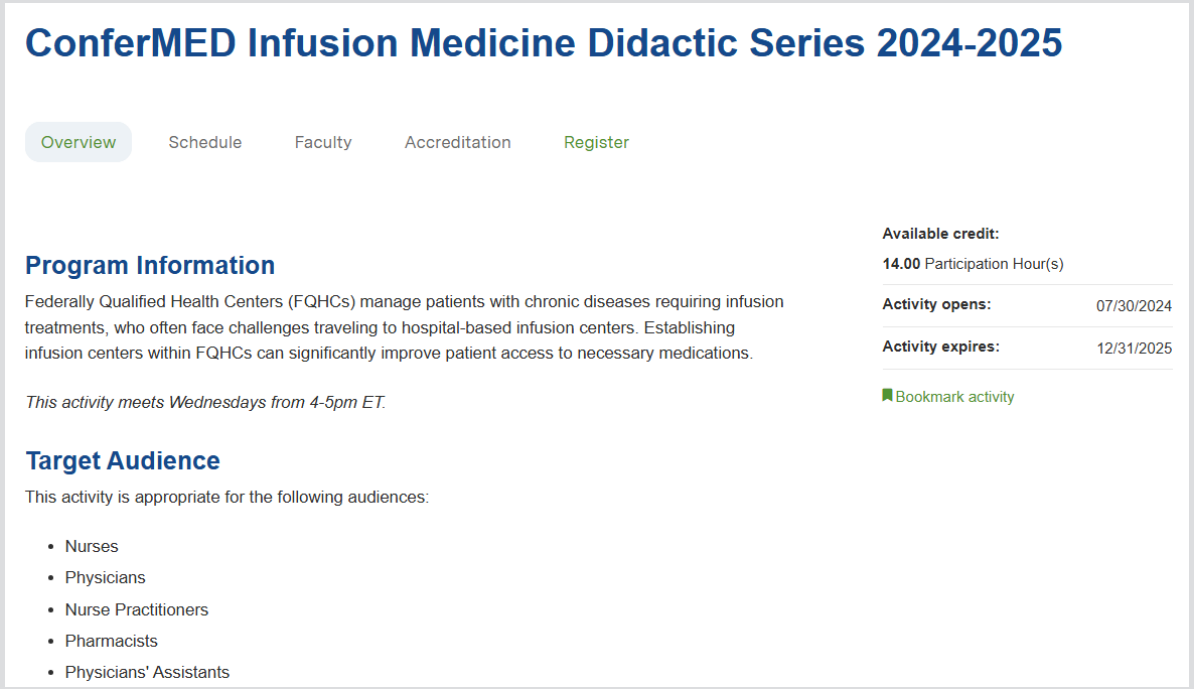
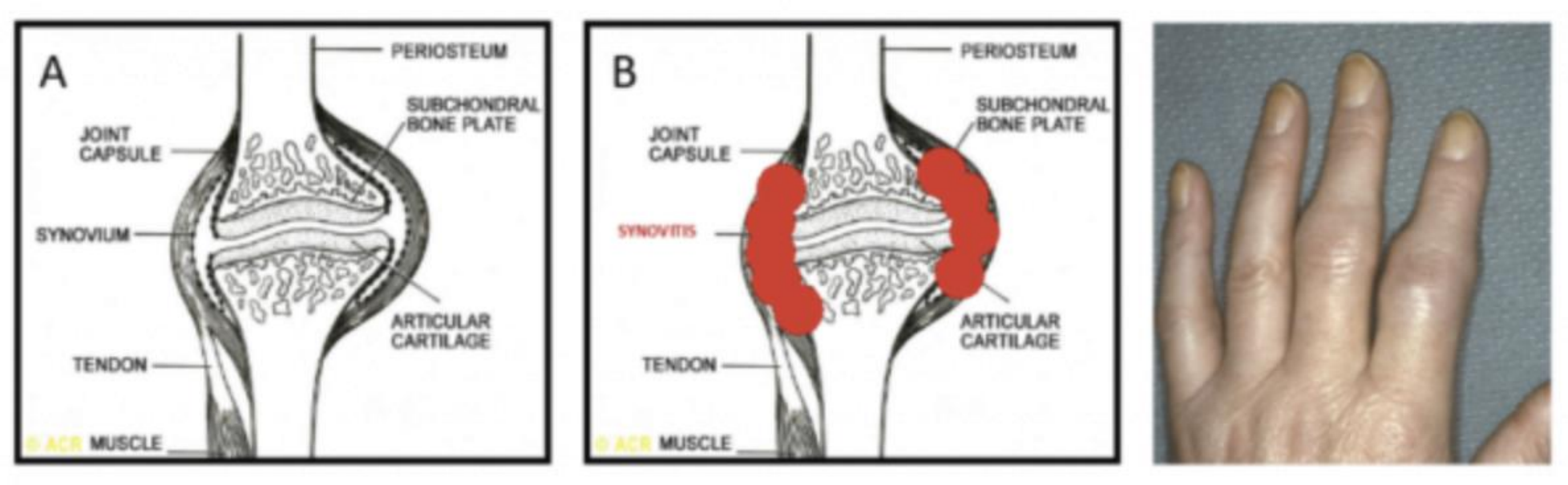


Infusion and In-Office TNFa-Inhibitor Therapy for Patients with Rheumatoid Arthritis Outline:

1. The role of **TNF-alpha** in Rheumatoid Arthritis pathogenesis
2. **TNF-alpha inhibitors** in the treatment paradigm of Rheumatoid Arthritis
3. **Infusion/In-Office products**: Infliximab (Remicade and biosimilars), Golimumab (Simponi Aria) IV, Certolizumab SQ
4. **Pre-testing**: Required and conditional
5. Factors which may influence choice: Specific clinical **contexts, contraindications**
6. **Guidance** in case of infection, elective surgery
7. eConsult case **examples**

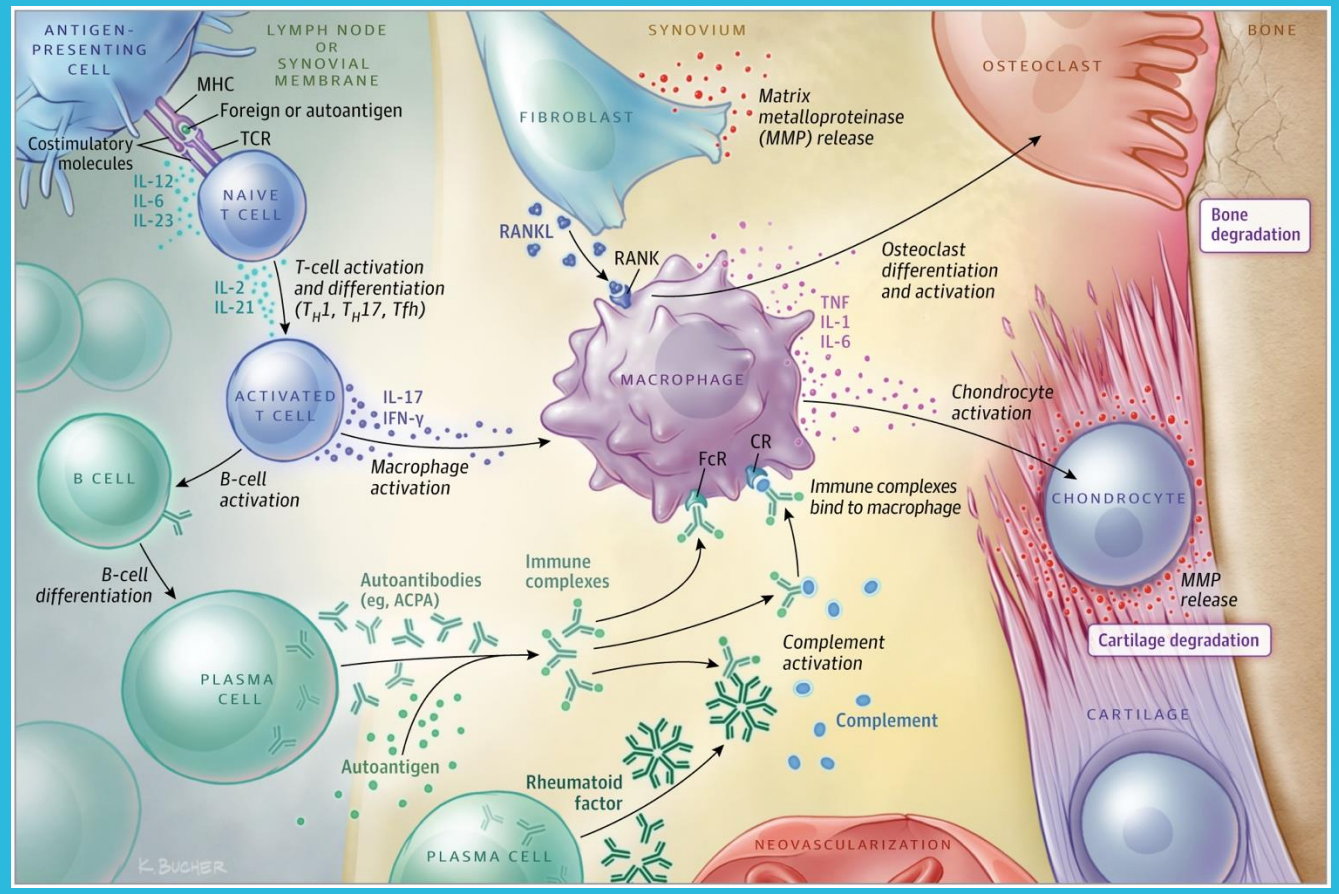
TNF-alpha in Rheumatoid Arthritis Pathogenesis



Rheumatoid Arthritis Synovitis

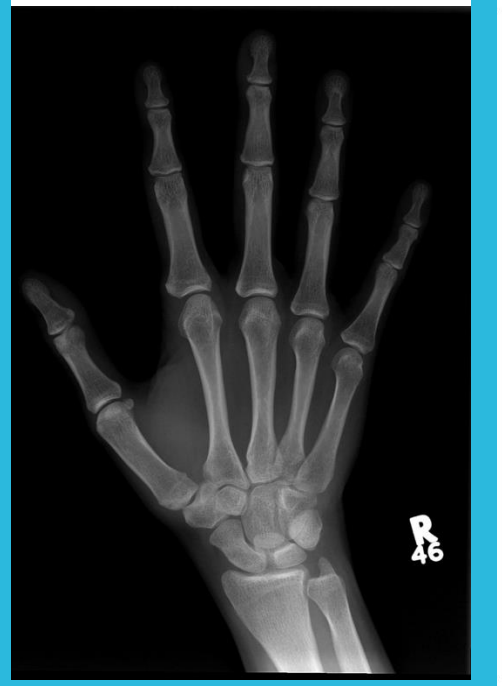
These images show a cartoon structure of a normal joint (A), Rheumatoid Arthritis "Synovitis" which is inflammation of the lining of the joint (B), and what synovitis looks like in a person who has Rheumatoid Arthritis.

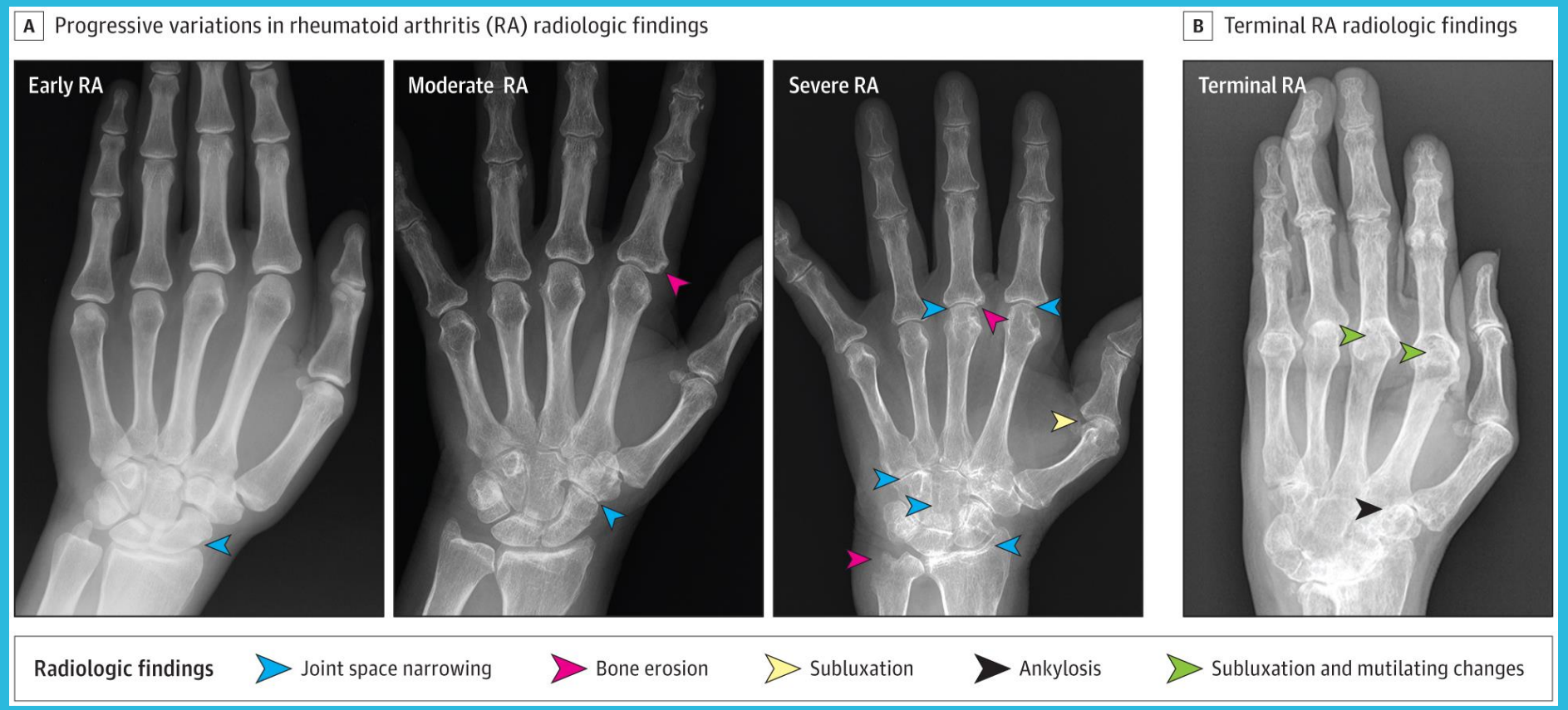
TNF-alpha in Rheumatoid Arthritis Pathogenesis



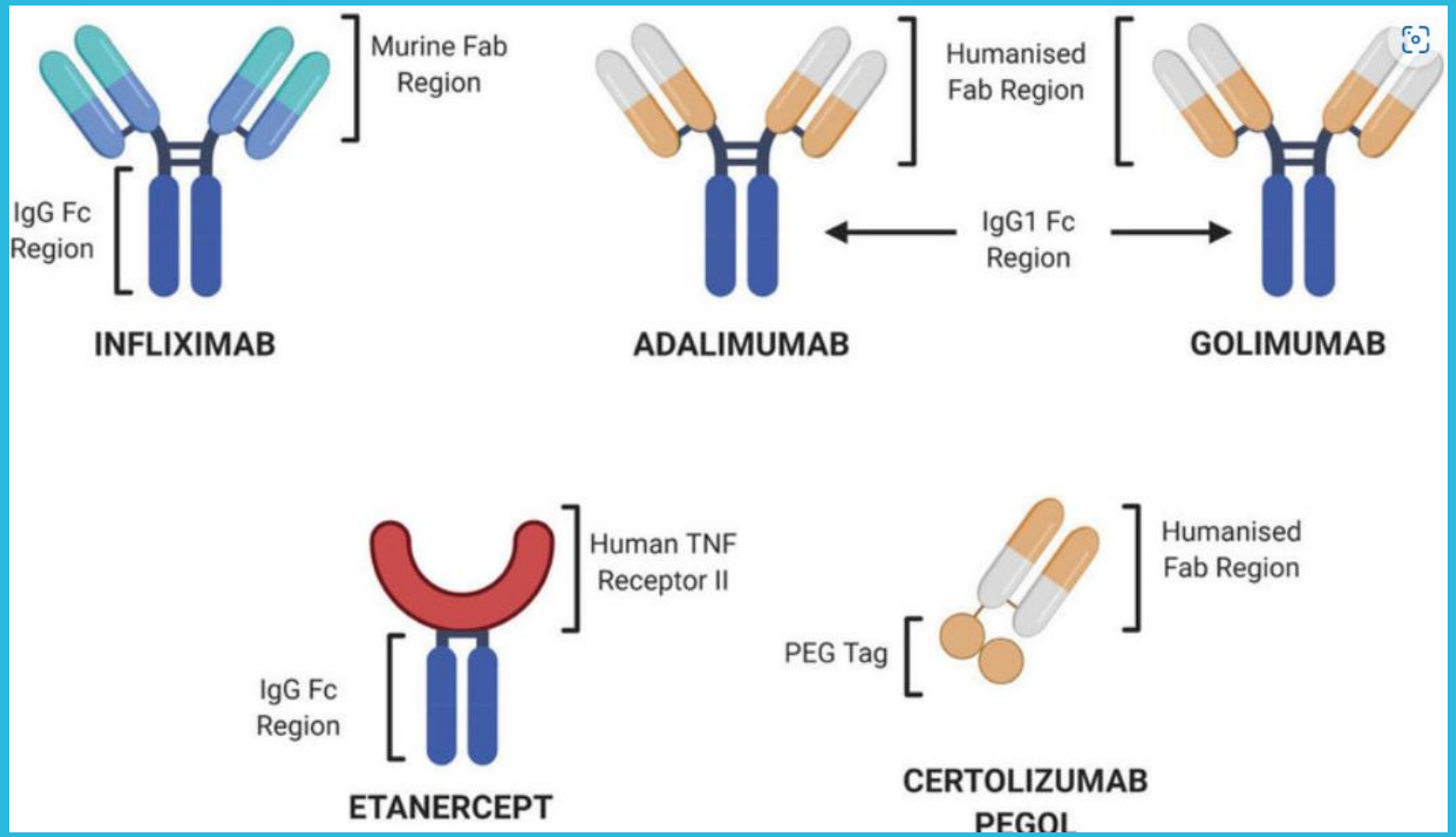
JAMA. 2018;320(13):1360-1372. doi:10.1001/jama.2018.13103

Normal Hand




A Progressive variations in rheumatoid arthritis (RA) radiologic findings
B Terminal RA radiologic findings
Early RA
Moderate RA
Severe RA
Terminal RA
Radiologic findings
Joint space narrowing
Bone erosion
Subluxation
Ankylosis
Subluxation and mutilating changes

TNF-alpha Inhibitors in the Treatment of Rheumatoid Arthritis



Names:
- **ximab** = chimeric (murine + human)
- **zumab** = humanized
- **umab** = fully humanized

Infliximab brands:
- **Remicade**
- **Inflectra**
- **Renflexis**
- **Ixifi**
- **Avsola**

Golimumab IV:
- **Simponi Aria**

Certolizumab Pegol:
- **Cimzia**

Patient Selection

Patient history:

- **Diagnosis of RA**. Document onset, objective findings (labs, imaging).
- **Current or prior treatment** with a csDMARD or documented contraindication (pregnancy/planning, childbearing age not on LARC, liver disease) or history of intolerance.

Confirm Moderate to Severely Active RA Disease activity:

- **CDAI**: https://www.mdcalc.com/calc/2177/clinical-disease-activity-index-cdai-rheumatoid-arthritis
- **SDAI**
- **DAS-ESR or DAS-CRP**

Infliximab IV Infusion

Indication: Adults with Moderate to Severely Active RA

- Concurrent treatment with Methotrexate (or Leflunomide) is advised.
- Initial dose: 3mg/kg week 0, week 2, week 6, then every 8 weeks.
- In case of a partial but inadequate treatment response after 12-16 weeks, the dose and the dose frequency can be adjusted with insurance approval.
  - Dose could be increased to 5mg/kg (max 10mg/kg).
  - Dose interval could be decreased to every 6 weeks, or every 4 weeks.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103772s5389s5391s5394lbl.pdf

Golimumab IV Infusion (Simponi Aria)

Indication: Adults with Moderate to Severely Active RA

- Used ***with or without*** a csDMARD such as Methotrexate or Leflunomide.
- Dose: 2mg/kg week 0, week 4, then every 8 weeks thereafter (fixed schedule).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125433s014lbl.pdf

Certolizumab Pegol (Cimzia) SQ injection in-office (AKA Cimzia-LYO)

Indication: Adults with Moderate to Severely Active RA

- Used ***with or without*** a csDMARD such as Methotrexate or Leflunomide.
- Loading doses: 400mg week 0, week 2, week 4, then—
- Maintenance dose (in office) 400mg every 4 weeks.
- In-office: Lyophylized powder kit to be reconstituted.

https://www.cimziahcp.com/formulations-dosing/in-office-injection

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125160s270lbl.pdf

Assessing for Synovitis

YouTube link: https://www.youtube.com/watch?v=KbU8pb1dcuI

Arthritis Research Canada. Joint exam to screen for inflammation. YouTube. https://www.youtube.com/watch?v=KbU8pb1dcuI

Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Subgroup and Type[a]	Molecular Target	Structure	Selected Adverse Event[b]	Efficacy (ACR70 Response Rates)[c]
Synthetic DMARDs				
Conventional[d]				
Methotrexate (10-25 mg/wk)	Unknown	Small chemical molecules (oral)	Nausea, stomatitis, liver enzyme level increase, bone marrow suppression, pneumonitis, teratogenicity	20-40%[49,50]
Sulfasalazine (2-4 g/d)	Unknown		Hypersensitivity reactions (mainly cutaneous), nausea, diarrhea, agranulocytosis, drug-induced lupus, azoospermia	No RCT data for 3 g daily; little modern data at all 8% at 2 g[51]
Leflunomide (20 mg/d)	Dihydroorotate dehydrogenase		Diarrhea, hypertension, hypersensitivity reactions, liver enzyme level in crease, leukcytopenia, teratogenicity	10%[51]
(Hydroxy-) chloroquine (**hydroxychloroquine**: 400 mg/d; **chloroquine**: 250 mg/d)	Unknown		Retinopathy	Unavailable

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Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Subgroup and Type[a]	Molecular Target	Structure	Selected Adverse Event[b]	Efficacy (ACR70 Response Rates)[c]
Biologic DMARDs				
Originator biologic[e]				
Etanercept (50 mg/wk)	TNF	Receptor construct	Infections, reactivation of tuberculosis, psoriasiform skin changes, exacerbation of demyelinating diseases, drug-induced lupus, nonmelanoma skin cancer, injection site or infusion reactions	20% (methotrexate insufficient responders) 12% (TNF inhibitor insufficient responders)[56]
Infliximab (3-10 mg/kg every 8 wk)	TNF	Chimeric monoclonal antibody		
Adalimumab (40 mg every 2 wk)	TNF	Human monoclonal antibodies		
Golimumab (50 mg/mo)	TNF	Human monoclonal antibodies		
Certolizumab (200 mg every 2 wk)	TNF	Fab' fragment of humanized monoclonal antibody		

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Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Subgroup and Type[a]	Molecular Target	Structure	Selected Adverse Event[b]	Efficacy (ACR70 Response Rates)[c]
Biologic DMARDs				
Originator biologic[e]				
Tocilizumab (162 mg/wk)	IL-6 receptor	Humanized monoclonal antibody	Infections, reactivation of tuberculosis, bowel perforation, hypersensitivity reactions, neutropenia, injection site reactions, hyperlipidemia	22% (methotrexate insufficient responders)[57] 12% (TNF inhibitor insufficient responders)[58]
Sarilumab (150-200 mg every 2 wk)	IL-6 receptor	Human monoclonal antibody		
Rituximab (100 mg every 6 mo)	CD20 (B-cell)	Chimeric monoclonal antibody	Hypersensitivity reactions, reactivation of hepatitis B, leukocytopenia	22% (methotrexate insufficient responders)[59] 12% (TNF inhibitor insufficient responders)[60]
Abatacept (125 mg/wk)	CD80/86 (costimulation)	Receptor construct	Infections, reactivation of tuberculosis, leukocytopenia, injection site reactions	22% (methotrexate insufficient responders)[61] 10% (TNF inhibitor insufficient responders)[62]

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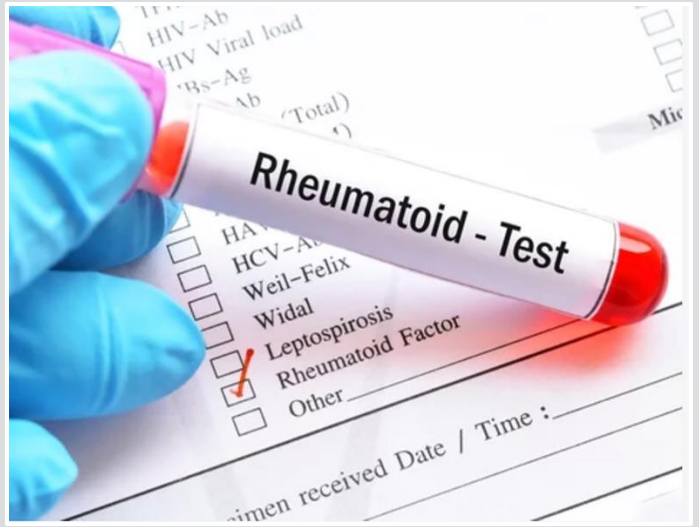
Patient Pre-Testing and Routine Monitoring

Patient Pre-Testing:

- Latent Tuberculosis screening: PPD, serum Quantiferon gold assay, Chest X-ray. If treated, try to obtain treatment records and monitor with yearly CXR.
- Hepatitis B Core antibody-total and Hepatitis B Surface Antigen (SAg).
- Hepatitis C Antibody w/ reflex.
- Consider HIV screen.



Routine Monitoring:

- CBC with diff and liver and kidney function every 3-6 months.
- ESR and CRP every 3-6 months for RA disease activity monitoring.

TNFa Contraindications

1. Active **infection** or history of severe/recurrent infections.
2. **Live vaccination** within 4 weeks of start date.
3. Symptomatic, activity-limiting **Congestive Heart Failure (CHF)**.
4. **Hematologic malignancy**: Lymphoma or leukemia.
5. **Autoimmune demyelinating disorder**—Multiple sclerosis (MS), Clinically Isolated Syndrome (CIS), Guillain-Barré syndrome (GBS), Chronic Demyelinating Inflammatory Polyneuropathy (CIDP).
6. History of **non-melanoma skin cancer**.

Patient Specific Factors

- **History of uveitis**; Infliximab and Simponi Aria may be favored over Certolizumab.
- **Women of child-bearing age** not using LARC; Certolizumab Pegol does not have an Fc-fragment and is often preferred in this context.
  - Least likely to cross the placental barrier.
  - Other TNFi are low-risk during the 1st-2nd trimesters and are commonly used as well.

eConsult Case Examples

Case #1:

50 year-old female patient with a history of RA just established primary care at the practice. She reports taking Methotrexate 15mg once a week, folic acid 1mg daily since her diagnosis around age 40.
She was receiving Infliximab infusions every 8 weeks from her Rheumatologist. She does not have Rheumatology care established locally. Her last Infliximab infusion was >12 weeks ago and she reports worsening joint pain and swelling.

Now what?

eConsult Case Examples

Case #1: Overdue for Infliximab infusion. *Now what?*

Recommended steps:

1. History and Exam
   - Document **RA history**: Approx age of onset/diagnosis, treatments tried and result.
   - Document **MSK exam and disease activity**.
2. Try to obtain her **prior Rheumatology records**.
3. **Testing**: ESR, CRP, CBC with diff, liver and kidney function, Hep B, Hep C, and TB screenings. Consider HIV, STI screening.
4. If no contraindications identified and TNFi therapy is appropriate, request **prior authorization**.
5. Common **RA flare remedies**: 3 week Prednisone taper (20mg x 5d, 15mg x 5d, 10mg x 5d, etc.), or IM (deltoid or gluteal) 80mg Methylprednisolone injection.

eConsult Case Examples

Case #2:

25-year-old female with early onset seropositive (RF, CCP Ab) RA diagnosed age 19. She has been treated with NSAIDs, intermittent Prednisone tapers and she has been treated with weekly Methotrexate as well as Etanercept (Enbrel) sq weekly. She shares that she has always struggled to remember to take her weekly etanercept and has self-injection anxiety. She also shared that she is in a long-term relationship and ***is not using any form of contraceptive***.

She feels that her RA is not well controlled and has 8 swollen and tender joints on exam.

eConsult Case Examples

Case #2: Pregnancy risk and doing poorly on Methotrexate and Etanercept

Recommended steps:

1. **Calculate her RA disease activity**: **https://www.mdcalc.com/calc/2177/clinical-disease-activity-index-cdai-rheumatoid-arthritis**
2. Review to ensure that her **screening labs** are up to date.
3. **Treatment options** given potential for a pregnancy and relative contraindication to MTX:
   - IV Golimumab (Simponi Aria); In-office, short (30 min) admin time and infrequent. No strong indication for concurrent MTX or Leflunomide.
   - Certolizumab Pegol (Cimzia-Lyo); In-office, quick SQ injection (no IV), no need for concurrent MTX or Leflunomide.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Questions?