PHARMACOLOGIC THERAPY IN RA

BY: SH.ASSAR

GENERAL PRINCIPLES

- Early recognition and diagnosis
- Care by an expert (rheumatologist)
- Early use of DMARDs for all patients diagnosed with RA
- Efforts toward tight control, utilizing a treat-to-target strategy, with a goal of remission or low disease activity
- Use of anti inflammatory agents, including NSAIDs and glucocorticoids, only as adjuncts to DMARD therapy

Pretreatment evaluation

- **General testing for all patients** :Baseline CBC,Cr, aminotransferases, ESR, CRP. In patients receiving interleukin 6 (IL-6) inhibitors and Janus kinase (JAK) inhibitors, lipids are also monitored.

- **Hepatitis virus screening** : In all patients without a known history of hepatitis, we screen for hepatitis B and C before initiating therapy with conventional DMARDs, including methotrexate (MTX) and leflunomide (LEF); biologic DMARDs; and JAK inhibitors.

- **Ophthalmologic screening** for hydroxychloroquine use

- **Testing for latent tuberculosis** : with PPD or an interferon-gamma release assay prior to all biologic DMARDs and prior to use of a JAK inhibitor
- chest radiograph in patients with a history of other risk factors for latent TB, even if screening tests are negative, given the risks of false-negative testing

Choice of therapy

- **based upon multiple factors, including:**
- Level of disease activity (eg, mild versus moderate to severe)
- Presence of comorbid conditions
- Stage of therapy (eg, initial versus subsequent therapy in patients resistant to a given intervention)
- Regulatory restrictions (eg, governmental or health insurance company coverage limitations)
- Patient preferences (eg, route and frequency of drug administration, monitoring requirements, personal cost, fertility planning)
- Presence of adverse prognostic signs

Drugs classified as disease-modifying antirheumatic drugs (DMARDs)

- Nonbiologic (traditional or conventional) DMARDs, including MTX, HCQ, sulfasalazine (SSZ), and LEF

- Biologic DMARDs, which are produced by recombinant DNA technology and generally target cytokines or their receptors or are directed against other cell surface molecules. such as the **TNF-alpha inhibitors etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol**; and the **IL-6 receptor antagonists tocilizumab and sarilumab,** T-cell costimulation blocker abatacept (CTLA4-Ig) and the **anti-CD20 B-cell depleting monoclonal antibody rituximab**

- **Targeted synthetic DMARDs, including several JAK inhibitors include tofacitinib, baricitinib, upadacitinib, filgotinib, and peficitinib**, which are orally administered small molecule DMARDs that inhibit cytokine and growth factor signaling through interference with JAKs

Approach to drug therapy

- In patients with active RA, we initiate anti inflammatory therapy with either a NSAID or glucocorticoid, depending upon the degree of disease activity, and generally start DMARD therapy with MTX. NSAIDs and systemic and intraarticular glucocorticoids can act rapidly to reduce disease activity, while DMARDs, including MTX, may take weeks to months to achieve optimal effects.

- Patients unable to take MTX may require an alternative agent, such as HCQ, SSZ, or LEF.

- In patients resistant to initial DMARD therapy (eg, MTX), we usually treat with a combination of DMARDs (eg, MTX plus SSZ and HCQ, or MTX plus a TNF inhibitor),

Assessment and monitoring

- Patients should be seen on a regular basis for clinical and laboratory monitoring of disease and for screening for drug toxicities
- Patient history
- Physical examination
- Laboratory monitoring of disease activity
- Imaging: use of these techniques for routine monitoring does not result in improved outcomes
- Drug monitoring and prevention of drug toxicity

DMARD THERAPY

- We initially use one of the more effective DMARDs, **usually MTX**, both to suppress synovitis and other signs and symptoms of active disease and to prevent articular bone erosions and joint space narrowing.
- initiate DMARD therapy as early in the treatment of RA as possible because delayed use results in poorer physical function and increased joint injury
- **MTX contraindications :**
- Women who are contemplating becoming pregnant or women not using adequate contraception
- Women who are pregnant
- Patients with liver disease or excessive alcohol intake
- Patients with severe renal impairment (eGFR< 30 mL/min)

MTX dosing

- MTX is given in a single weekly dose, usually orally
- initiating therapy at a dose between **7.5 and 15 mg once weekly** for most patients, depending upon the degree of disease activity, the size and age of the patient, the presence of comorbidities, and renal function
- The MTX dose is increased as tolerated and as needed to control symptoms and signs of arthritis
- MTX dose is increased as tolerated and as needed to control symptoms and signs of arthritis. Our usual approach is to increase the dose after four weeks by 2.5 - 5 mg per week at intervals no more frequent than every month

- For patients in whom 15 to 25 mg of MTX orally once weekly is ineffective or is poorly tolerated because of GI symptoms, a trial of subcutaneous MTX administration is an alternative to switching to another DMARD or to adding other conventional DMARDs or a tumor necrosis factor (TNF) inhibitor

- MTX treatment requires meticulous monitoring for **bone marrow, liver, and lung toxicity.**

- Randomized head-to-head trials have found that MTX has a **faster onset** of action, comparable or **greater efficacy**, .MTX has also been shown to **improve survival**

- Combinations of MTX with either sulfasalazine or hydroxychloroquine, with both sulfasalazine and hydroxychloroquine (commonly referred to as "triple therapy"), or with a biologic DMARD also have proven efficacy for initial treatment of highly active RA in patients with poor prognostic features

resistance to initial therapy with nonbiologic DMARDs

- Failure to achieve remission or low disease activity within **three to six months** of initiating MTX or other DMARD therapy in maximally tolerated doses within the usual therapeutic range
- A requirement, for **chronic glucocorticoid therapy in a dose of > 5 -7.5 mg/day** of prednisone or equivalent to achieve or maintain remission or low disease activity after 3-6 months of treatment with DMARDs
- A requirement for multiple courses of treatment with glucocorticoids, in excess of doses used for chronic therapy, for the treatment of **recurrent disease flares** in patients whose medication doses have been increased to the maximally tolerated or acceptable level
- Continued **progression of erosive disease** or structural damage that is not accounted for by prior mechanical destabilization of the joints

- In patients resistant to MTX after three to six months of treatment at optimal doses and route of administration (usually 25 mg/week), we suggest either the use of **DMARD "triple therapy" with MTX plus SSZ and HCQ, or the combination of continued MTX plus the addition of TNF inhibitor**

- In patients with partial responses or showing progressive improvement, we may continue therapy with MTX for >3 months before switching to one of these approaches, particularly in those with low to moderate levels of disease activity and with limited functional impairment. Another option would be **switching from oral to subcutaneous MTX** to see if the response could be enhanced

- We prefer triple therapy with MTX, SSZ, and HCQ in patients for whom personal drug cost, regulatory restrictions on the use of biologic agents and JAK inhibitors, or preference for an oral nonbiologic agent, rather than an injectable, is an important factor

Triple DMARD administration and dosing

- MTX is continued at the maximum tolerated dose achieved with initial therapy up to 25 mg once weekly
- SSZ is gradually increased from 500 mg twice daily to 1000 to 1500 mg twice daily.
- HCQ is used at a dose of 400 mg daily in most patients but should not exceed 5 mg/kg/day calculated on the basis of real body weight

resistance to initial therapy with nonbiologic DMARDs

- there is no convincing evidence that any one of the TNF inhibitors has greater efficacy than the others

- who unable to use a TNF inhibitor and who have a high level of disease activity, we suggest the combinations of MTX plus abatacept, tocilizumab, or a JAK inhibitor as alernatives to a TNF inhibitor

- in patients who are unable to use a biologic agent or JAK inhibitor because of regulatory or cost considerations or other factors, we suggest either **switching from MTX to LEF or adding LEF to ongoing MTX**

Methotrexate plus rituximab

- Rituximab is another alternative that may have similar efficacy to a TNF inhibitor in patients with seropositive RA, but regulatory restrictions may limit its availability before a TNF inhibitor has been tried

- Rituximab is a reasonable alternative for patients with a prior lymphoproliferative malignancy

- We generally administer rituximab as an IV infusion of 1000 mg, repeated once 2 weeks later, together with ongoing weekly MTX. Courses of rituximab are typically administered approximately every six months

DURATION OF THERAPY

- Most patients with early, severely active rheumatoid arthritis (RA) require sustained therapy and adjustments in their treatment regimen over months to years to achieve treatment goals

- In the minority of patients who achieve a sustained clinical remission of **greater than one year**, we cautiously try to reduce nonbiologic and biologic DMARD doses

- we generally **avoid discontinuing all DMARD treatment**, and there are insufficient data to prospectively identify which patients will be able to successfully reduce or discontinue therapy without clinical recurrence or radiographic progression

Thanks for your attention