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Review Article

Disease-Modifying Drugs for Rheumatoid Arthritis. When, How and Which One to Use

Asif Hussain,[1-3] Jawaria Avais[2]

[1]Clinical Examiner for Australian Medical Council, [2]Epping Medical Specialist Centre
[3]Editor Surgical Archives

Abstract

Rheumatoid arthritis is the most common rheumatological disease worldwide, with many articular and extra-articular complications associated with comorbidities and mortality. Cardiac and pulmonary complications contribute the most towards morbidity, mortality and pose great difficulty in RA management. Recently there have been many updates in the pharmacological options available for rheumatoid arthritis, including biological and targeted biological disease-modifying drugs.

This review article focuses on the pros and cons of the main therapeutic options currently used to manage rheumatoid arthritis according to the updated guidelines by EULAR. The report also encompasses a summary of the recent guidelines by EULAR.

Keywords: Rheumatoid arthritis, conventional Disease Modifying Anti Rheumatoid Drugs, Biological DMARD, Targeted DMARDs.

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Corresponding Author: Dr. Asif Hussain **Email:** drasifhussain@gmail.com

Introduction

Basic Principles of Treatment for Rheumatoid Arthritis (RA)

1): Start the disease-modifying drugs as soon as the diagnosis is made. Delay causes more complications, disability, treatment failure, and morbidity, Multidisciplinary team approach combining pharmacological and non-pharmacological approach is essential1 [Fig,1 &2].

2): Treat to Target (T2T) approach has a better outcome. Target should be remission or at least the lowest disease activity (LDA) achievable.2

3): Patient-centred approach where decisions are guided by the clinician's joint input and the patient's informed choice.

4): NSAIDs and Glucocorticoids (GC) are mainly used for symptom control. GC should be used as minimum as possible (both duration and dosage) to bridge the gap caused by the delayed onset of action of disease-modifying anti rheumatoid drugs (DMARD). Long-term side effects of GC therapy should be avoided by using DMARD therapy.[3]

5): First DMARD to start is usually Methotrexate (MTX) unless it's contraindicated or gives intolerable side effects.[4]

6): If T2T is not achieved by the maximum tolerable dose of MTX within six months or MTX is not tolerated or MTX is contraindicated, then other conventional synthetic DMARD (csDMARD) such as Leflunomide (Lef), Sulfasalazine (SLZ), Hydroxychloroquine (HCQ) alone or in combination can be added on to MTX or can substitute MTX.[5]

7): If csDMARD monotherapy or combination therapy (with or without MTX) are not effective for T2T within six months or a patient has poor prognostic factors, then adding on biological DMARD (bDMARD) or targeted synthetic DMARD (tsDMARD) should be considered. Poor prognostic factors include high baseline disease activity or bone erosions, or positive antibodies in the blood. Choice b/w various bDMARD or tsDMARD is based on adverse effects, comorbidities, availabi-

lity, cost, and local guidelines.5

8): Failure of one bDMARD or tsDMARD to achieve T2T within six months should lead to substitution by another bDMARD of the different class (or same class) or tsDMARD. RTX is generally reserved when other bDMARD &/or tsDMARD fail to achieve T2T5-7 [Fig.1].

9): Aggressive control of cardiovascular (CVS) risk factors, osteoporosis prevention & treatment, clear setting up targets and goals of treatment, drug-related side effects, especially infections, involvement of allied health team (physiotherapist and occupational therapist), & patient education about disease and treatment is an essential part of the whole treatment plan.[5]

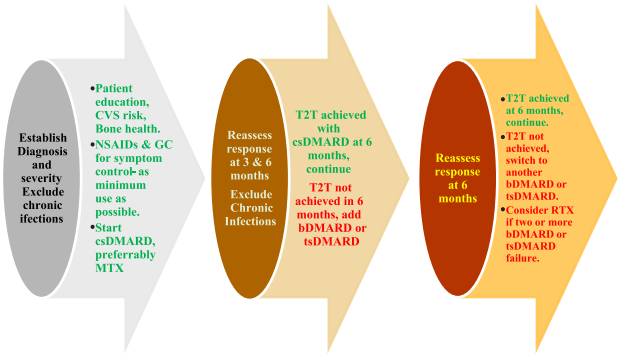

Fig.1: *Flowsheet of an Incremental Treatment Plan for Rheumatoid Arthritis:*
Abbreviations used: CVS (Cardiovascular), DMARD (Disease Modifying Anti Rheumatoid Drugs), bDMARD (biological DMARD), csDMARD (conventional synthetic DMARD), GC (Glucocorticoids), MTX (Methotrexate), NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), RTX (Rituximab), T2T (Target to Treat), tsDMARD (Targeted Small Molecule DMARD).

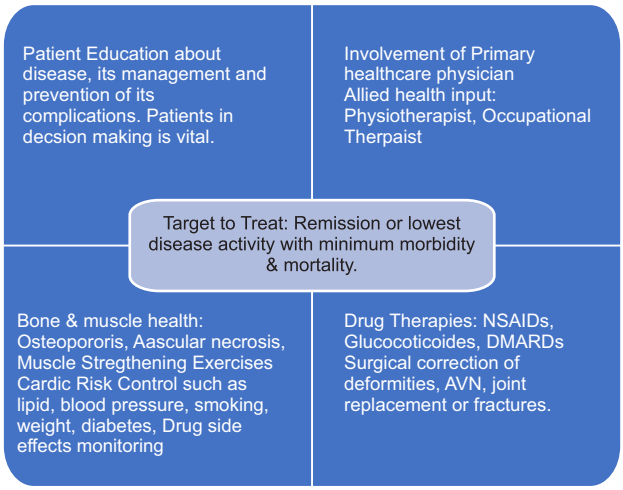

Fig.2: *Multidisciplinary Team Approach Along with Pharmacological and Non-Pharmacological Modalities for Rheumatoid Arthritis*

Conventional Synthetic DMARD (csDMARD):

Methotrexate (MTX):

It works by anti-folate and reduced thymidine & purines synthesis. It also works as immunosuppressive by increasing adenosine signalling activity and controlling cytokines and immune cell functions. This is why it still works despite folate replacement which is used to minimize the side effects. Generally, it is started as 10-15 mg/week and optimized to the maximum of 25 mg/week. Subcutaneous is more effective as it has more bioavailability & it can also avoid some of the GIT side effects. Folate is given at a dose of 5 mg/ week other than when MTX is taken. The dose of folic acid can be increased to minimize the side effects primarily related to GIT and the liver. If the side effects are there, the dose of MTX can also be reduced or can be given as two divided doses per week.[8]

It's used as first-line Disease Modifying Anti Rheumatoid Drugs (DMARD) when the diagnosis of RA is established as it's the most effective, more tolerated, and cost-effective among all csDMARD[5]. Also, the long-term experience and safety profile is well established for MTX. Even when a patient is a candidate for biological DMARDs (bDMARD) or targeted synthetic DMARD (tsDMARD), it's still preferred to continue MTX as it gives better outcomes and minimizes the immunogenicity against biological agents. If MTX is not tolerated, is inadequate, or is contraindicated, then other csDMARD such as Leflunomide, Hydroxychloroquine (HCQ), &/or sulfasalazine (SLZ) can be used as well. These can be used either in combination with MTX or as an alternative to MTX. If MTX is not adequate for a target to treat the rheumatoid disease activity, then either csDMARD is added, or a patient may need biological DMARDs or targeted synthetic DMARD. Patients with high disease activity, radiological bone erosions, or positive antibodies often need bDMARD or tsDMARD if csDMARD is ineffective[9,10] [Tab 1].

Leflunomide (Lef):

It blocks mitochondrial enzyme Di-Hydro Orotic Acid Dehydrogenase (DHODH), which is a rate-limiting enzyme for pyrimidines synthesis and affects lymphocytic proliferation as lymphocytes need eight times more pyrimidine before starting cell division. Other cells can escape this effect to some extent by increasing uptake of pyrimidines and using salvage pathway. It absorbed almost completely with non-enzymatic conversion into its active metabolite Teriflunomide. More than 99% of the drug is bound with plasma proteins, and its half-life varies from 5-40 days. Its metabolite can be found in the blood even after two years of dis-

continuation of the drug. Its excreted half in urine and half in bile. Dose adjustment is rarely needed in renal failure; however, caution should be exercised when eGFR is less than 15. It's used at 10-20 mg/day. A loading dose of 100mg may be used for the first few days as it helps to expedite the effect, but it can increase the side effects too. Half-life is long, and metabolites can be found in the blood even after 1-2 years of stopping the drug. It's also used for psoriatic arthritis, though it's not very effective for cutaneous psoriasis. It can be combined with bDMARD or tsDMARD, especially as an alternative to MTX if later is not tolerated or is contraindicated[11] [Tab 1].

Sulfasalazine (SLZ)

It's an antibacterial and immunosuppressive drug. It's used as an alternative to MTX or an adjunct to MTX. Dose is 0.5-2gm/day. It's safe in pregnancy.[5,11]

Hydroxychloroquine (HCQ)

It's an immunomodulator, antithrombotic and anti-inflammatory drug that works by alkalinizing the lysosomal pH in macrophages. Other mechanisms include effect on cutaneous dendrocytes, which have an important role in lupus, increased endothelial nitric oxide, inhibition of platelet aggregation and arachidonic acid pathway, inhibition of antiphospholipid-beta^2 microglobulin on macrophages, inhibition of phospholipase enzyme. It deposits in various tissues, including skin, liver, retina. In addition, it also binds with melanin in the skin and retina. It's used as an alternative to MTX for mild RA or can also be added as an adjunct to MTX if later is not adequate. It's also used as a must part of SLE treatment (Systemic Lupus Erythematosus) unless it's contraindicated due to its beneficial effect on SLE, Antiphospholipid syndrome, lupus-related osteoporosis, lupus nephropathy, and metabolic benefits of lowering cholesterol and glucose. HCQ is also used for cutaneous lupus, antiphospholipid syndrome, primary Sjogren's syndrome, sarcoidosis, and skin manifestations of dermatomyositis. The dose is often 100-400 mg/day. It's safe in pregnancy, and patients are encouraged to continue HCQ in pregnancy due to its effect in reducing relapse of SLE during pregnancy[11] [Tab 1].

Overlapping Side effects of csDMARD

GIT upset: it's common side for MTX, Leflunomide & Sulfasalazine. Nausea, diarrhea &/or pain are common symptoms. MTX commonly causes nausea, and Leflunomide causes diarrhea. Splitting the MTX dose or reducing the dose can help. Leflunomide can be taken with food, and dose reduction may be needed.[12]

Liver derangement: MTX & Lef are notorious for causing liver derangement, which is dose and duration dependent, and dose reduction or temporarily holding the drug may help. Liver enzymes monitoring is essential. Fatty liver patients with normal enzymes and normal liver function tests can use MTX but will need monitoring. Alcohol and other hepatotoxic factors should be controlled. Combining Lef with MTX or NSAIDs or other hepatotoxic drugs increases the

Table 1: *Chemical Synthetic Disease Modifying Anti Rheumatoid Drugs (csDMARD):*

Drug	Mechanism	Dose	Use	Main Side Effects
Methotrexate	Anti-folate, Adenosine signalling Controls Cytokine & immune cell functions control	10-25mg/week, PO	First-line DMARD in RA	Hepatotoxic Pneumonitis, ILD Pancytopenia GIT mucosal damage Hair loss Teratogenic
Hydroxychloroquine	immunomodulator, antithrombotic and anti-inflammatory	100-400mg daily, PO.	Monotherapy for Mild RA Combination with other csDMARDs.	Retinal toxicity Skin discoloration QT prolongation
Leflunomide	Blocks mitochondrial enzyme Di-Hydro Orotic Acid Dehydrogenase (DHODH) & hence pyrimidines synthesis	10-20 mg daily, PO	Alternative to MTX or combined with other DMARDs, including MTX	Same as Methotrexate PLUS Hypertension, Neuropathy Effect on male fertility.
Sulfasalazine	antibacterial and immunosuppressive	0.5-2gm, PO daily	Alternative to MTX or combined with other DMARDs, including MTX.	Allergic skin rash, Idiosyncratic hepatitis, pneumonitis or neutropenia, or hemolytic anemia.

Abbreviations: DMARDs (Disease Modifying Anti Rheumatoid Drugs), gm (gram), GIT (Gastro-Intestinal Tract), ILD (Interstitial Lung Disease), mg (milligram), PO (Per Oral), MTX (Methotrexate).

chance of liver insult[12]. Any other pre-existing liver disease would require hepatology team advice. Folate can help if MTX causes liver-related side effects. Leflunomide-related liver dysfunction, especially ALT rise up to 2 times above upper normal, can be managed by reducing the dose. However, ALT increase more than two times may need stopping the drug, and if it's persistent, Lef washout will be required. Screening for HBV, HCV, pre-existing liver disease is essential before starting these medications. Sulfasalazine can cause hepatitis as an idiosyncratic reaction. This will need stopping the drug.[13]

Bone marrow suppression: MTX, Lef, and Sulfasalazine all-cause marrow suppression and cytopenia to a variable extent. Monitoring with a complete blood count is essential. Folate replacement reduces MTX-related cytopenia, and dose reduction/cessation may be needed if it doesn't work. Leflunomide-related mild neutropenia will improve with dose reduction. However, severe neutropenia (ANC<1) will need stopping the drug and may also need to wash out if it doesn't improve. Sulfasalazine can also cause idiosyncratic hematological side effects, which would warrant permanent cessation of therapy.[12,13]

Pneumonitis is a common side effect of MTX, but Lef can also cause pneumonitis. Patients with pre-existing lung disease such as COPD or ILD or lung nodules are at higher risk of MTX-related lung toxicity. It's better to avoid MTX if there is lung disease but can be used with caution if the disease is mild and stable. Leflunomide can cause pneumonitis, and the risk is higher in smokers or those with pre-existing ILD or when used with MTX. However, causative relation is not established with Leflunomide, and one possibility is that these drugs increase rheumatoid-related lung disease. Sulfasalazine can cause allergic pneumonitis, which would need a cessation of the drug.[13]

Teratogenic effects: MTX and Lef are teratogenic and are contraindicated in pregnancy. MTX should be stopped 3-6 months before conception and should use effective contraceptive methods to avoid pregnancy while being on MTX. Folate should continue before and during pregnancy[14]. MTX-related effect on male fertility is not established. Leflunomide should be stopped six months before pregnancy. Lef washes out with Cholestyramine (8gm TDS for at least 11 days but can be needed longer if the blood level of teriflunomide is still detectable). Activated Charcoal can also be used for washout at 50gm QID for 11 days[15]. Leflunomide also affects male fertility too, and the patient should use effective contraception while being on Leflunomide and for a minimum of six months after stopping it. Sulfasalazine and HCQ are relatively safe in pregnancy. Folate should be given with Sulfasalazine, and the dose should not exceed 2gm/day.[16]

Perioperative: MTX can be continued perioperatively in most cases. Those at risk of pneumonia, such as COPD / ILD patients or those with perioperative fall in renal functions, may need withholding treatment. Those on high doses (25mg/week) will also require temporary dose reduction. Leflunomide has a very long half-life, and hence temporary cessation is not recommended. If a patient is at high risk of infection or a significant surgery warrant stopping Leflunomide, it will need Leflunomide to wash out. Sulfasalazine, being a short-acting & minimally immunosuppressive drug, is generally not required. However, if there is any potential interaction with other medications used, then it can be held on the day of surgery.[13-16]

Specific side effects of csDMARD

Leflunomide can also cause neuropathy and hypertension. The main adverse effects are GIT upset such as diarrhea and pain. The second common adverse events are skin rash, itching, and other effects. Less common but more severe side effects include hepatic dysfunction, bone marrow depression, neuropathy, hypertension, or pneumonitis. Some of its side effects (hepatic and pulmonary) are due to aryl hydrocarbon receptor activation. Dose reduction or stopping the drug may be needed. Washout of the drug for serious adverse effects like hepatotoxicity, bone marrow depression, preconception, before major surgery, etc., is required by using activated Charcoal (50gm QID for 11 days) or Cholestyramine (8gm TDS for 11 days). However, the washout can increase the risk of disease flare-up. Patients who have a history of using Leflunomide in the past two years should have teriflunomide levels checked before becoming pregnant. If it's still detectable, it will also need to wash out till the level is undetectable before becoming pregnant. In countries where drug level is not available, empirical washout may be an option.[17,18]

Hydroxychloroquine (HCQ)

Major risk factors for HCQ toxicity include old age, high dose of more than 5mg/kg/day, renal or hepatic dysfunction causing reduced clearance. In addition, pre-existing eye disease is a risk factor for retinal complications & similarly, pre-existing myocardial disease is a risk for heart issues. Drugs causing prolong QTc can also add on to prolonged QTc due to HCQ. It can cause dose & duration-dependent cataract and retinal deposition-related side effects, requiring regular eye check-ups. The drug should be stopped if there is any sign of retinopathy. Degeneration of the pigment layer of the retina is seen due to the binding of the HCQ with the pigments. The classic pattern can be a bull's appearance. Significant issues are retinal toxicity

with damage to the pigment layer of the retina and related complications such as cystoid macular degeneration etc. Those with risk factors for retinopathy should be assessed at baseline and then at least annually. Optical Coherent Tomography (OCT) and visual field assessment are needed. Retinal toxicity usually occurs after long-term use. It is almost 20% at 20 years of use and then increases 4-5% every year. Hence baseline check-up before starting HCQ is needed to exclude any pre-existing retinal issues. Those without any risk factor will need reassessment after 4-5 years and then annually onward.[19]

Skin pigmentation due to HCQ should stop the medication. Other skin issues due to HCQ are dryness, itching, skin rash, worsening of cutaneous psoriasis, Steven-Johnson, and Toxic Epidermolysis Necrosis. Cardiotoxicity is another issue causing lysosomal dysfunction related to myocardial dysfunction and conduction defects. Baseline ECG is essential to assess QTc. Those at risk will need further assessment such as ECG, Echocardiography, and Holter. It can also cause myotoxicity presenting with weakness.20 Neurotoxicity, partly contributed by lysosomal dysfunction, is another possibility, including seizures, psychiatric manifestations, cinchonism-like effects, &/or headache. HCQ is not considered an immunosuppressant drug. Instead, it's an immunomodulator drug, and infection risk is not high while using HCQ. HCQ can also cause hypoglycemia and lowers cholesterol by HMG-CoA Reductase inhibition. Quinacrine is a lesser toxic option for those who can't tolerate HCQ.[20,21]

Sulfasalazine can cause sulfasalazine allergy and skin rash Sulfasalazine related idiosyncratic hepatitis, pneumonitis, or hematological side effects (neutropenia or hemolytic anemia) need immediate discontinuation of the drug.[22]

Biological DMARD (bDMARD) & Targeted Synthetic (tsDMARD)

Tumour Necrosis Factor-Alpha Inhibitors (TNFi):

Infliximab is a chimeric murine/human monoclonal IgG 1 antibody. It binds with both soluble and membrane-bound TNF-alpha. The dose is 3-5mg/kg infusion given at 0,2,6 weeks, and then every two months. Side effects of TNF drugs include drug-related lupus, increased risk of lymphoma, and infections, especially TB reactivation. Adverse effects are similar to other TNFi and include infections (bacterial. Viral, TB, fungal), malignancies (lymphoma), antibodies against drug, autoimmunity & hypersensitivity, injection site reactions, cardiac failure, neurological (demyelination, etc.)[23] [Tab 2].

Etanercept (ETN) is a recombinant fusion protein humanized antibody with Fc part of human IgG1 with soluble TNF-Alpha receptors. It binds with the TNF receptor and prevents TNF-mediated cellular response. The dose is 25 mg subcutaneous (s.c) twice a week or 50 mg weekly. Adverse effects are similar to other TNFi and include infections (bacterial. Viral, TB, fungal), malignancies (lymphoma), antibodies against drug, autoimmunity & hypersensitivity, injection site reactions, cardiac failure, neurological (demyelination, etc.)[24]

Adalimumab (Humira) is humanized recombinant monoclonal IgG1 antibody which binds with both soluble and membrane-bound TNF-Alpha with a high affinity. The dose is subcutaneous injection twice a week. The dose is 40mg s/c twice a month. Adverse effects are similar to other TNFi and include infections (bacterial. Viral, TB, fungal), malignancies (lymphoma), antibodies against drug, autoimmunity & hypersensitivity, injection site reactions, cardiac failure, neurological (demyelination, etc.).[25]

Golimumab is also a humanized monoclonal IgG1 antibody that binds with both soluble and membrane-bound TNF-alpha. The dose is a subcutaneous injection of 50 mg once a month and can be increased to 100 mg if there is no response after four doses (in a patient with a body weight of >100kg).[26]

Certolizumab-Pegol (CZP) is a recombinant Fab part of IgG1 against TNF-alpha attached with Peg instead of Fc part of IgG-1, which prolongs its half-life it can be used twice a month. Dose is 400mg s/c at 0,2 & 4 weeks, followed by 200mg s/c every fortnight or 400 mg monthly. Because it lacks the Fc part of IgG (unlike other anti-TNF antibodies), its active transport at the placenta is not there, and only a small amount can cross the placenta by passive diffusion. This is why it's relatively safer in pregnancy and lactation.[24] Also, due to the lack of Gc portion, it doesn't bind with complement and doesn't cause antibody-mediated cytotoxicity. Unlike other TNF inhibitors, it also doesn't cause degranulation of neutrophils. However, like Infliximab and adalimumab, it blocks endotoxin (LPS) mediated TNF and IL-1 production. Due to PEG, it is likely distributed more to inflammation sites (more than Infliximab and Adalimumab). PEG is excreted through the kidneys. Adalimumab Etanercept and CZP can be used in juvenile idiopathic arthritis as well. Antibodies against CZP affect its availability and activity. Concomitant MTX reduces anti CZP antibodies. The subcutaneous dose has 80% bioavailability. Adverse effects are similar to other TNFi and include infections (bacterial. Viral, TB, fungal), malignancies (lymphoma), antibodies against drug, autoimmunity & hypersensitivity, injection site reactions, cardiac failure, neurological (demyelination, etc.). Deranged LFTs have been reported as well.[27]

CTLA-4 Inhibitors (Abatacept)

Its fusion protein humanized Fc part of IgG1 and extracellular part of CTLA-4 (Cytotoxic T Lymphocytic Antigen-4). CTLA-4 will bind with CD80/86 on antigen-presenting cells (APCs) and inhibit its binding with C28 on T lymphocytes. Thus, Abatacept prevents T cell activation and also inhibits B cell activation. But this also reduces immunity against cancers & infections. Hence, there is a risk of increased malignancy, especially lymphoma. However, it's a known fact that RA patients are at increased risk of lymphoma; hence it's not clear how much Abatacept plays its role. It's once a month dose. Abatacept can also be used for juvenile idiopathic polyarthritis[28] [Tab 2].

IL-6 Antagonists (Tocilizumab & Sarilumab)

These are humanized recombinant monoclonal IgG1 antibodies against the IL-6 receptor. Tocilizumab (TCZ) is given monthly infusion at 8mg/kg or can be used as a weekly subcutaneous dose of 162mg/week. Both have almost similar efficacy and side effect profiles. CRP may not rise as IL-6 is needed for the liver to make CRP.[24,26]

CD-20 Blockers (Rituximab, RTX)

It's chimeric Maurine-human monoclonal IgG-1 antibody against CD-20 on Pe-B cells, B-cells, and memory B-cells in circulation and causes B- cell depletion and reduces antibodies in the blood (hypo or agammaglobulinemia), hence increasing the risk of infections too. However, it doesn't affect the early stages of B-cells and doesn't affect plasma cells; therefore, it doesn't reduce autoantibodies. Its role for immunosuppression could be due to either reduced conversion of B-cells into plasma cells or reduced role of B-cells as antigen-presenting cells. Effect on other B-cells outside the circulation, such as those in the synovium, etc., is variable. The impact on pre-B cells and mature B-cells in circulations lasts for 6-9 months. Hence, it's a good choice for those where frequent injections/ medications may be an issue. Also, for the same reason, the cycle is repeated after six months [Tab 2].

As it depletes B-cells, it's also used for patients with B-cell malignancies, though the dose is higher. The dose for RA cases is 1 gm IV infusion, which is repeated in 2 weeks. This cycle is repeated every six months. Dose for vasculitis may differ (375mg/square meter/ week for four weeks, and the same dose is used for lymphoma). Specific side effects include HBV reactivation and increased risk of JC Virus infection-related progressive multifocal leukoencephalopathy (PML). Three particular diseases of concern with RTX include HBV, PML (1;20000), and PJP. Screening for HBV and PML is needed before starting RTX. Hence, in addition to routine screening done for all biological drugs, the patient should be tested for immunoglobulins level at baseline, JC virus, and HBV. PJP infection risk is 1.5-6% and can happen even if CD-4 cell counts are above 200 when a patient is on RTX. This could be due to the loss of B-cell support for Th-cells. Prophylaxis with Bactrim is often used when a patient is on RTX. Infusion-related side effects are very common (30-45%), and premedication with 100mg hydrocortisone or methylprednisolone, antihistamine, and paracetamol are used. Neutropenia is also common with RTX treatment.[29]

Uses of RTX in rheumatology are RA which is refractory to other bDMARD with positive autoantibodies or those with a history of B-cell lymphoma. Other than RA, RTX is used for SLE (nephritis, Micro Angiopathic hemolytic Anaemia, ITP, Antiphospholipid syndrome, Cerebritis, etc.), especially when other options are not working. It's also used for ANCA-Associated (MP-3) Wegner's or Microscopic polyangiitis (AAV), Idiopathic inflammatory Myositis (Polymyositis, Dermatomyositis, Inclusion body myositis, Anti-Synthetase Syndrome), Scleroderma (it helps skin, ILD, joints in SSc), SS related systemic issues such as vasculitis or ILD. It's contraindicated in active infections (acute or chronic), heart failure (NYHA III&IV), hypersensitivity to RTX or mouse proteins, and pregnancy.

IL-1 Inhibitors (Anakinra)

Anakinra is an IL-1 inhibitor and short-acting drug with a half-life of 4-6 hours; hence it needs daily 100 mg subcutaneous injection. It's not as effective as other biological drugs for RA. Its primary use is for inflammatory diseases like polyserositis, adult-onset Still's disease, or gout.

Targeted Synthetic DMARD (tsDMARD) / Janus Kinase Inhibitors (JAKi)

JAK is an intracellular part of the receptors for various interleukins (1,2, 4,6,7,9,15&21), interferons, and other cytokines. Once the receptors bind with its ligand, JAK gets activated (phosphorylation) and causes activation (phosphorylation) of STAT (Signal Transducer and Activation of Transcription), which then leads to cytokines production and inflammation. JAK-inhibitors stop this process and control inflammation.[30]

These are small molecules that can cross the cell membrane and bind with intracellular JAK. The small size also makes them easily cross the placenta and hence cause issues in pregnancy. Tofacitinib (JAK 1&3) and Baricitinib (JAK 1&2) are two approved drugs in this group. Tofacitinib dose is 5 mg BD and is primarily metabolized in the liver; hence it can be used in renal failure cases but will need dose reduction if the eGFR is <30. Baricitinib is mainly excreted through kidneys, and therefore, the dose needs to be reduced from 4 mg

OD to 2 mg OD in CKD cases when eGFR is below 60 & it shouldn't be used if eGFR is below 30 ml/min.[31]

Screening & vaccination for bDMARD & tsDMARD:

Patients should be screened for any infection such as HBV, HCV, & Tuberculosis. Anyone having any of these should be treated first before starting bDMARDs. HBV should be treated if RTX is to be started irrespective of its HBsAg status, and the hepatology team should be involved in the care. For other biological options, HBV should be treated if HBsAg is positive. Otherwise, close monitoring with blood tests for HBV and LFTs is essential. Screening for JC Virus is necessary before starting on RTX. Screening for JAK inhibitors includes infections. Blood counts, lipid profile, renal functions,

Table 2: *A summary of Biological DMARDs & Targeted DMARDs.*

Drugs	Mechanism	Dose	Use	Main Side effects
Infliximab; chimeric murine/human monoclonal IgG 1	TNF-inhibitor	3-mg/kg Infusion 0,2,6 weeks then every 2 months	Mod to severe RA	Infections, cytopenia, potential teratogenicity, Injection site reactions, autoimmunity, drug-related lupus, Demyelinating disease, Lipid disorder, and liver derangement. Risk for lymphoma. Worsens heart failure.
Adalimumab: humanized recombinant monoclonal IgG1	TNF-a inhibitor	40mg, s/c twice a month	As above	As for Infliximab. Autoimmunity is lesser as it's humanized.
Certolizumab-Pegol: recombinant Fab part of IgG1 against TNF -alpha attached with Peg instead of Fc part of IgG-1	TNF-a inhibitor	400mg s/c at 0,2 & 4 weeks, followed by 200mg s/c every fortnight or 400mg monthly	As above	As above. Relatively less teratogenic potential. The placental crossing is minimal due to the lack of Fc part of IgG1.
Golimumab: humani zed monoclonal IgG1	TNF-a inhibitor	50 -100 mg, s/c, monthly	As above	As for Infliximab. Autoimmunity is lesser as it's humanized.
Etanercept: fusion protein having Fc part of human IgG1 with soluble TNF-Alpha receptors	TNF-a inhibitor	25mg, subcutaneous (s.c) twice a week or 50 mg weekly	As above	As above. The infection risk is slightly less.
Anakinra	IL-1R blocker	100 mg s/c injection, daily	As above	Injection site reactions, infections, and cytopenia it's not commonly used for RA.
Tocilizumab: humanized recombinant monoclonal IgG1 antibodies	1L-6R blocker	monthly infusion 8mg/kg or weekly s/c dose of 162mg/week	As above	Above PLUS bowel perforation
Abatacept: fusion protein humanized Fc part of IgG1 and extracellular part of CTLA-4.	CTLA-4 blocker		As Above	Injection-related side effects, infections, and risk of lymphoma. Pregnancy-related data is not conclusive
Rituximab: chimeric maurine-human monoclonal IgG -1 antibody	Anti-CD 20	1000mg infusion at 0 & 2 weeks, repeated 6monthly.	Usually for RA resistant to other bDMARD or lymphoma.	Infections PML, HBV reactivation B-cell depletion, Hypo/agammaglobulinemia Neutropenia.
Tofacitinib:	JAK inhibitor	5mg BD	As for TNF inhibitors	Infections, hypertension, headache, GIT upset, hypercholesterolemia, and deranged LFTs, DVT/PE

Abbreviations used: BD (Twice a day), CTLA-4 (Cytotoxic T-Lymphocyte Antigen-4), DVT (Deep Venous Thrombosis), GIT (Gastro-Intestinal Tract), HBV (Hepatitis B Virus), IgG (Immunoglobulin G), IL-1R (Interleukin-1 receptor), IL-6R (Interleukin-6 receptor), JAK (Janus Kinase), LFTs (Liver Function Tests), mg (milligram), PE (Pulmonary Embolism), PML (Progressive Multifocal Leukoencephalopathy), RA (Rheumatoid Arthritis), s/c (subcutaneous), TNF-a (Tumour Necrosis Factor-alpha).

and LFT monitoring are required.

Vaccination for HAV, HBV, HPV, influenza, pneumococcus and other age-related infections should be given before starting bDMARD. Patients on neurological should avoid alive vaccines. Children born to mothers on biological drugs should not be given any alive vaccine until six months of age as all these biological drugs do cross the placenta and can pose a risk to the newborns.[5]

Vaccines against influenzas, pneumococcus, HAV & HBV are given 4-6 weeks before starting RTX treatment. Tetanus vaccine often doesn't work if someone is using RTX. If needed, the patient should be given passive immunization with anti-tetanus immunoglobulins if required within six months of the previous dose of RTX. Immunization with live vaccine is contraindicated for those on RTX treatment, or newborns should be delayed for six months if the mother was given RTX after 20 weeks of pregnancy. Also, the risk of maternal and newborn infections increases when RTX is used in the second half of pregnancy. It should be avoided in pregnancy as safety data is not adequate.

Efficacy of bDMARD & tsDMARD

All TNFi, Abatacept, JAK inhibitors are efficacious for moderate to severe RA not responding to csDMARD and can be used depending on side effects profile, comorbidities, availability, and local guidelines. If a patient fails to respond to one biological drug, another biologic of the same class or preferably a different class can be tried. RTX is generally reserved for those who fail to respond to other biological drugs with/without csDMARD. RTX is also preferred if there is a current or past history of B-cell malignancies.[5]

Overlapping Side effects of bDMARD &tsDMARD

Teratogenicity / unknown safety during pregnancy
Most biologics are IgG and are actively transported across the placenta by receptors for the Fc part of maternal IgG on placental tissues. The second but less important mechanism is passive diffusion across. Certolizumab doesn't have an IgG Fc component; it can only cross the placenta by passive diffusion. The level of Infliximab and adalimumab in fetal blood were 1.5 times higher than the maternal level. However, the CZP level is 3-5% of the maternal level. Few studies have shown no increased risk of pregnancy with CZP.TNF inhibitor-related data shows that women exposed to TNFi during pregnancy have similar rates of issues such as preterm delivery, miscarriage, and congenital anomalies as those in women with rheumatoid arthritis without TNF inhibitor treatment. Most of these biological drugs are not safe in pregnancy as data is limited. Tocilizumab can cause teratogenicity in animals. Certolizumab-Peg is relatively safer. However, enough data is not available to support the safety or document toxicity for many of these biological drugs.[32,33]

Leucopoenia or thrombocytopenia is expected as these suppress the functioning of cytokines. TNFi, Anakinra, B- cell depletion is common with RTX. Agammaglobulinemia is also common with RTX.[33]

Infections are especially very common, including bacterial infections such as pneumonia, multi-dermatomal zoster, reactivation of TB, etc. Vigilance is needed to detect and treat fever, and other inflammatory clues may be masked. Tocilizumab & Abatacept has the highest risk of infections. But other biological agents also have an increased risk of diseases [32,33,34].

Lipid disorder is also common with TNFi, Tocilizumab, and JAKi.[32,33] Monitoring for other CVS risk factor is important.

Liver derangement is common with many of the DMARDs and needs monitoring.[34] Rising transaminases three times or above upper limit of normal will need to stop the drug.

Injection site reactions such as pain, redness, and swelling are common and can be managed with a cold pack, antihistamine, and topical steroid. Infusion-related reactions can cause hypotension, angioedema, bronchospasm, and skin rash. These may be IgE-mediated anaphylaxis type, but mostly anaphylactoid reactions can be managed by slowing the infusion rate. Delayed reactions due to serum sickness can cause arthralgia, rash, fever, etc., and usually due to anti-drug antibodies, more with chimeric molecules.[35]

Autoantibodies against TNFi, RTX and other bDAMRD including against humanized antibody molecules are common. Loading dose and concomitant MTX reduces auto-antibodies production. They reduce available drugs and their effectiveness as well. HACA and HAHA (Human Antibodies against Chimeric Antigen, & Human Antibody against Humanised Antigens) are the terms used.[36-37]

Specific Side Effects

TCZ: diverticulosis-related bowel perforations. Patients at risk of bowel disease should avoid TCZ. Any abdominal pain or GI symptoms in patients on TCZ should be investigated on an urgent basis. Inflammatory markers, significantly CRP, may not rise. Other side effects are liver abnormalities, lipid derangement, infections, and cytopenia.[38]

Abatacept: Injection-related side effects, infections, and risk of lymphoma. Pregnancy-related data is not conclusive.[33,35]

RTX: the infusion-related reaction is very common and almost 30-50% cases have hypotension, dyspnoea,

skin rash, etc., especially with the first dose. Agammaglobulinemia and B-cell depletion are common. HBV reactivation is a significant concern and should be treated irrespective of HBsAg status. Data is not conclusive regarding pregnancy.[39]

Infliximab & TNFi: Drug-related autoantibodies formation, especially against Infliximab, is typical as it's chimeric. It will reduce efficacy and response to a drug. It can also cause a serum sickness type reaction (arthralgia, fever, rash, etc.). Risk is low if immunosuppressive therapy such as MTX is used concomitantly. Drug-related lupus is also another concern with TNFi, especially Infliximab. Demyelination is also another risk which means any history of demyelinating disease is a contraindication for TNFi. Lymphoma & malignancy risk also increases with TNFi. Treating with TNFi is not recommended in patients with heart failure (NYHA Class III & IV).[32-34]

Anakinra causes injection site reactions, infections, and cytopenia as common side effects. There is not enough data regarding pregnancy.[36,37]

JAK inhibitor's side effects: Tofacitinib can cause an increased risk for Infections, hypertension, headache, GIT upset, hypercholesterolemia, and deranged liver enzymes are common. Tofacitinib can also increase the risk of DVT/PE (YAMAOKA K). Baricitinib causes hypercholesterolemia which gets better when a dose is reduced, or statins are added. Neutropenia and infections are also common. JAK inhibitors are contraindicated if there is an infection, neutropenia, severe liver disease, or pregnancy. Due to short half-life, these can be continued until the day before surgery and should be held until wound healing is complete.[40]

Conclusion:

Early start of csDMARDs, preferably MTX, is vital to prevent complications and morbidity within three months of diagnosis. If there is no response to csDMARD within six months, adding on bDMARD or tsDMARD is needed. There is no particular preference for any bDMARDs. The selection of bDMARD depends on comorbidities, side effect profile, and availability. RTX is used mainly for bDMARD resistant seropositive rheumatoid or those with a history of lymphocytic malignancy.

Conflict of interest

None

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None

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