Dosing & Monitoring of Rheumatologic Medications in Patients with Renal Disease

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Drug Categories:

- NSAIDS
- Corticosteroids
- DMARDS (Disease Modifying Anti Rheumatoid Drugs)
- Targeted Synthetic DMARDS
- Biologic DMARDS
- IL6R Inh
- T-Cell Co-stimulation Inh
- B-Cell Depleting Agents
- IL 17-23 Pathway Inh
- SLE Drugs
- Gout Drugs
- Chronic Management

NSAIDS:

- **Non-selective NSAIDs**
- Diclofenac – Diflunisal – Etodolac – Fenoprofen – Flurbiprofen – Ibuprofen – Indomethacin – Ketoprofen – Ketorolac - Mefenamic acid – Meloxicam - Nabumetone - Naproxen - Oxaprozin - Piroxicam - Sulindac - Tolmetin
- **COX-2 Selective NSAIDs**
- Celecoxib - Rofecoxib - Valdecoxib

NSAIDS:

- NSAIDs lower the amount of blood that flows through the kidneys. So, they can lead to acute kidney injury (AKI) and/or worsening CKD, especially at higher doses and/or with long-term use.
- People with CKD should avoid NSAIDs, especially if estimated glomerular filtration rate (eGFR) is lower than 60.
- However, a systematic review of seven studies found no association with progression of CKD for regular-dose NSAID use, although a significantly increased risk of progression from high-dose use.

NSAIDS

- Recommended monitoring includes a CBC, renal tests, and hepatic panel. These recommendations are from the American College of Rheumatology for use in rheumatoid arthritis patients who use NSAIDs chronically and who have no comorbidities nor history of complications. Monitoring is less common in patients not considered high risk for NSAID toxicity. However, NSAIDs are either contraindicated, or their use requires monitoring in patients with liver or renal problems.

Corticosteroids:

- Prednisone: no dosage adjustment
- Methylprednisolone: no dosage adjustment
- Hydrocortisone: no dosage adjustment
- Dexamethasone: no dosage adjustment

- Monitoring:
  - Direct measurement of drug level

Corticosteroids:

- The healthcare team should be aware of the possibility of adrenal suppression in all patients on corticosteroids, particularly those on supraphysiologic doses, for more than two weeks.

- Clinicians should consider bone mineral density (BMD) testing at baseline and after one year of corticosteroid therapy along with height measurement and screening for any fragility fractures. Subsequent assessments can then be pushed out to every 2 to 3 years if stable at one year.

DMARDS:

- MTX: Elimination is reduced in kidney failure.
- Sulfasalazine: no dosage adjustment
- Leflunomide: no dosage adjustment
- Hydroxychloroquine: no dosage adjustment

MTX monitoring:

- According to KDIGO guidelines, the dose of methotrexate should be reduced when the patient's glomerular filtration rate (GFR) <60 mL/min/1.73 m^2.
- Methotrexate should be avoided for patients with a GFR <15 mL/min/1.73 m^2.
- This toxicity is primarily due to the crystallization of methotrexate in the renal tubular lumen.

MTX monitoring:

- Patients taking methotrexate should undergo laboratory testing with complete blood count, serum creatinine, and transaminase level monitoring weekly for the first 4 weeks and then at least bimonthly.
- Creatinine clearance requires monitoring to avoid possible nephrotoxicity; a CrCl of 50 mL/min is necessary before prescribing methotrexate.

Sulfasalazine:

- Sulfasalazine-induced cytopenia, nephrotoxicity and hepatotoxicity is uncommon during long-term treatment. Some guidelines recommend 3 monthly monitoring blood tests indefinitely during long-term treatment while others recommend stopping monitoring after 1 year.

leflunomide

- Liver function tests
- CBC
- Blood pressure
- Pregnancy
  - Leflunomide black box label warning warrants periodic monitoring of hepatic enzymes every four weeks for the initial six months and every other month after that.

Hydroxychloroquine

- Titrating daily dose to achieve therapeutic benefits associated with whole blood HCQ >1000 ng/mL while 3) minimizing cumulative exposure by keeping levels <2000 ng/mL.

Targeted Synthetic DMARDS:

- Tofacitinib: RA indications: IR 5mg BD , ER 11 mg Daily.

No dose adjustment in CKD or ESRD. Administer after dialysis

It should be discontinued when lymphocyte count is less than 500.

ANC<500 discontinue the drug.

- Baricitinib:
  - GFR>60 no dose adjustment. (2mg daily)
  - GFR 30-60 1mg once Daily,
  - GFR<30 not recommended

- Upadacitinib: no dose adjustment

Tofacitinib monitoring:

	AT BASELINE	AFTER 4 TO 8 WEEKS	EVERY 3 MONTHS THEREAFTER
LYMPHOCYTES[a]	✓		✓
NEUTROPHILS	✓	✓	✓
HEMOGLOBIN	✓	✓	✓
LIPIDS[b]		✓	
LIVER ENZYMES	Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations are recommended		

AVOID INITIATION OF XELJANZ TREATMENT IN PATIENTS WITH:	Lymphocyte count <500 cells/mm^3	Absolute neutrophil count <1000 cells/mm^3	Hemoglobin levels <9 g/dL	Severe hepatic impairment

Laboratory Measures for the Treatment With Baricitinib

	Before Treatment Initiation	During Routine Patient Management	Monitoring at Week 12
Tuberculosis screening	Yes		
Hepatitis screening in accordance with clinical guidelines	Yes		
Complete blood count w/differential			
ANC	Yes	Yes	
ALC			
Hb			
Hepatic transaminases (ALT, AST)	Yes	Yes	
Lipids			Yes
Glomerular filtration rate	Yes		

Biologic DMARDS:

- TNF Inh:
  - Etanercept: no dose adjustment
  - Infliximab: no dose adjustment
  - Adalimumab: no dose adjustment
  - Certolizumab: no dose adjustment*
  - Golimumab: no dose adjustment

Infliximab monitoring:

- Infliximab is administered as an infusion with a dosing interval ranging from 2 to 16 weeks. Infusion of a standard dose of Infliximab leads to highly variable inter-individual serum drug concentrations partly due to the development of anti-Infliximab antibodies that bind to Infliximab leading to loss of therapeutic effect.

- Infliximab level >1 µg/mL is regarded as therapeutic
  Infliximab level ≤1 µg/mL is regarded as sub-therapeutic.

Biologic DMARDS:

- IL6 Receptor Inh:
  - Tocilizumab: no dose adjustment
    - Monitor lipids 4-8 weeks after initiation and then every 6 month.
    - Monitor LFT 4-8 weeks after initiation and then every 3 month.
    - Monitor neutrophils 4-8 weeks after initiation and then every 3 month.
    - Monitor platelets 4-8 weeks after initiation and then every 3 month.
  - Sarilumab: no dose adjustment

Biologic DMARDS:

- T Cell Co-Stimulation Inh:
  - Abatacept: no dose adjustment
  - No specific laboratory or immunological tests are needed to monitor abatacept therapy

Biologic DMARDS:

- B Cell Depleting Agents:
  - RTX:
    - If there was renal impairment before initiating the drug no dose adjustment.
    - If increasing creatinine witnessed discontinue the drug.
  - For patients taking rituximab, comprehensive laboratory monitoring should include hepatitis B screening before initiation, complete blood count with differential at baseline and every 2-4 months during treatment, and immunoglobulin levels at baseline and every 6 months to prevent serious complications.

Short-Term Monitoring (First 6 Months)

- CBC with differential: Every 2-4 months
- Monitor for rituximab-induced neutropenia which typically develops after a median of 10 weeks
- Pay special attention to platelet counts in patients with ITP

Long-Term Monitoring

- CBC with differential: Continue every 2-4 months throughout treatment
- Immunoglobulin levels: Every 6 months
- Particularly important for patients receiving multiple courses of rituximab
- Low baseline IgG level (<3 g/L) predicts greater risk of secondary immunodeficiency

- Post-Treatment Monitoring
  - **CBC with differential**: Continue for 6-12 months after completion of rituximab therapy.
  - **Immunoglobulin levels**: Monitor for at least 6 months after completion, especially in patients who developed hypogammaglobulinemia during treatment.
  - **HBV DNA levels**: Continue monitoring for 12 months after rituximab discontinuation in patients with positive hepatitis B serology.

Biologic DMARDS:

- IL 17/23 Pathway Inh
  - Secukinumab: no dose adjustment
  - Ixekizumab: no dose adjustment
  - Ustekinumab: no dose adjustment
  - Guselkumab: no dose adjustment

SLE Drugs:

- Azathioprine:
  - GFR>30: no dose adjustment
  - GFR 10-30: 75 to 100 % of usual dosage
  - GFR<10: 50 to 100% of usual dosage
  - On Dialysis: 50 to 100% of usual dosage

SLE Drugs:

Azathioprine:

Patients with low TPMT(thiopurine S-methyl transferase) activity have elevated 6-TGN (6-thioguanine nucleotide) when treated with standard doses of AZA and are at greatly increased risk of myelosuppression. Whereas patients with very high TPMT activity are either resistant to thiopurine drugs due to shunting of AZA down the 6-MMP pathway or require a high dose to achieve efficacy, but at the risk of hepatotoxicity due to high 6-MMP concentrations.

Myelosuppression can occur after 3 month of initiation.

SLE Drugs:

- MFM:
  - Immediate post transplant: no dose adjustment
  - GFR>25: no dose adjustment
  - GFR<25: no dose adjustment. not to exceed 1g twice daily and 720 mg twice daily
  - Dialysis: no dose adjustment. not to exceed 1g twice daily and 720 mg twice daily
  - Watch closely for leukopenia, Anemia, GI Symptoms

SLE Drugs:

- Cyclophosphamide:
  - Overally:
    - GFR>30 no dose adjustment
    - GFR 10-30 75 to 100% of normal dose
    - GFR<10 50 to 75 % of normal dose

SLE Drugs:

- CX for GPA:
  - Low dosed regimen:
    - GFR>100 : 2mg/kg
    - GFR 50-100 : 1.5 mg/kg/day
    - GFR 25-50 : 1.2 mg/kg/day
    - GFR 15-25 : 1 mg /kg /day
    - GFR<15 : 0.8 mg/kg/day

SLE Drugs:

- CX for GPA:
  - Pulse dose regimen:
    - <60 years GFR>30 : 15 mg/kg GFR<30 : 12.5 mg/kg
    - 60-70 years GFR>30 : 12.5 mg/kg GFR<30 : 10 mg/kg
    - >70 years GFR>30 : 10 mg/kg GFR<30 7.5 mg/kg

SLE Drugs:

- CX for lupus nephritis IV:
  - Low dose regimen:
    - 500 mg every 2 weeks for 6 doses
    - No dose adjustment
  - Higher dose regimen:
    - 500 to 1000 mg/m2 GFR>30 No dose adjustment
    - GFR<30 reduce to 500 mg/m2

SLE Drugs:

- Cyclophosphamide:
  - As cyclophosphamide can cause myelosuppression, it should not be used in patients with lab values of neutrophils of 1500/mm^3 or less and platelets less than 50000/mm^3.
  - Before the induction of cyclophosphamide treatment, any urinary obstructions should be corrected or excluded. Urinalysis is also a recommendation to evaluate for the presence of hematuria, proteinuria, or bacterial infections. Patients also require monitoring for signs and symptoms of cardiotoxicity, pulmonary toxicity, and history of pre-existing cardiac disease. These tests may include tests for cholesterol, lipids, and triglycerides.
  - As an immunosuppressive agent, cyclophosphamide toxicity correlates with the development of leukopenia, thrombocytopenia, and anemia.

SLE Drugs:

- Cyclosporin:
  - IN RA
    - Do not use with prior abnormal kidney function
    - If Cr increases about 30% of pretreatment Cr Decrease to 25 to 50% and if Cr rising continues discontinue the drug.
  - In Nephrotic syndrome:
    - If serum creatinine increases about 30% after treatment, decrease dose to 25 to 50% .
  - Hemodialysis: no supplemental dose is necessary
- Tacrolimus:
  - No initial dose adjustment.

SLE Drugs:

- Cyclosporine:
  - regular monitoring of liver function tests is advised in patients with hepatic impairment. Moreover, hypertension is a frequent adverse effect, necessitating blood pressure monitoring. To avert the potential risk of life-threatening hyperkalemia, the recommendation is to opt for an antihypertensive medication that does not belong to the category of potassium-sparing diuretics. During the initial 3 months of monitoring, it is recommended to assess blood urea nitrogen and creatinine levels for patients on a bi-weekly basis. Furthermore, regular monitoring of complete blood count, lipid profile, magnesium, and uric acid levels is advised for patients under chronic cyclosporine therapy for psoriasis.

SLE Drugs:

- Voclosporin:
  - If patient has prior renal impairment:
    - GFR>30 : no dose adjustment
    - GFR<30 15.8 mg twice daily
  - If GFR reduction occurs during treatment:
    - GFR<60 and reducing from baseline by >20% and <30% reduce dose to 7.9 mg BD.
    - GFR<60 and reduced >30% from baseline discontinue therapy and reassess GFR in 2 weeks and if enhanced restart with lower dose.

SLE Drugs:

- Voclosporin:
  - Obtaining a baseline GFR and subsequently measuring GFR every 2 weeks during the initial month, followed by measurements every 4 weeks thereafter, is advised. Furthermore, clinicians should consider measuring urinary protein excretion as clinically indicated. Moreover, baseline blood pressure monitoring, followed by measurements every 2 weeks during the initial month, is mandatory. In addition, conducting electrocardiograms and regularly monitoring potassium levels in patients are of significant importance.

Gout Drugs:

- Acute:
  - Colchicine:
    - Indications: Behcet Syndrome, CPP Crystal Arthritis, FMF, Gout Prophylaxis, Gout treatment, Pericarditis, Post pericardiotomy syndrome, Sweet syndrome, Vasculitis,
  - NSAIDS:
  - Corticosteroids:
- Chronic:
  - Allopurinol:

    GFR>60 no dose adjustment
  - Febuxostat:
    - GFR>30 no dose adjustment
    - GFR<30 20-40 mg Daily
    - Dialysis : no supplemental dose
  - Probenecid: GFR< 30 Avoid use
  - Pegloticase: no dose adjustment

CrCl	Gout flare, treatment	Gout flare, prophylaxis	Familial Mediterranean fever	Off-label indications
30 to 80	No dosage adjustment necessary.	No dosage adjustment necessary. Alternatively, some experts limit the dose to 0.6 mg daily in patients with CrCl 30 to 60 mL/minute.	No specific dosage adjustments are recommended; however, use of a reduced dose should be considered.	No specific dose adjustments recommended
<30	Consider alternate therapy (preferred). If alternate therapy is not available/tolerated, the following adjustment is recommended:1.2 mg at the first sign of flare, followed in 1 hour with a single dose of 0.6 mg; repeat treatment should not occur for at least 14 days. Alternatively, some experts recommend a single dose of 0.3 mg at the first sign of flare only; repeat treatment should not occur for at least 3 to 7 days.	Consider alternate therapy (preferred). If alternate therapy is not available/tolerated, the following adjustment is recommended:0.3 mg once daily (or 0.6 mg every other day); titrate only if necessary and with extreme caution. Maximum: 0.6 mg/day.	Initial: 0.3 mg once daily; titrate in 0.3 mg increments. Risk of toxicity is high; monitor closely. Maximum: 1.5 mg/day.	No specific dose adjustments recommended

Colchicine

Gout Drugs:

- Colchicine:
  - Colchicine has a narrow therapeutic index; however, no blood test is available to determine its serum concentration. Colchicine accumulation is associated with severe and fatal adverse drug reactions, especially in patients with hepatic or renal impairment or those taking a P-glycoprotein or CYP3A4 inhibitor. Parameters that require monitoring include a complete blood count and renal and hepatic function tests. Patients should be advised to report signs and symptoms of colchicine toxicity, including nausea, vomiting, diarrhea, and abdominal pain.

Allopurinol

eGFR mL/minute/1.73 m2	**Suggested initial dose**
>30 to 60	50 mg daily
>15 to 30	50 mg every other day
5 to 15	50 mg twice **weekly**
<5	50 mg once **weekly**

Gout Drugs:

- Allopurinol:
  - Complete blood count, liver function tests, renal function, and serum uric acid levels shall be measured every 2 to 5 weeks while titrating the dose until achieving the target serum uric acid level and every six months thereafter. Patients need counseling about the signs and symptoms of AHS(Allopurinol hypersensitivity syndrome) with a recommendation to discontinue allopurinol promptly if they develop skin rash concerning AHS, especially early in therapy.

Osteoporosis & hypercalcemia treatment:

- Vitamin D: no dose adjustment
- Calcium:
  - Calcium carbonate : in GFR<25 dose adjustment may be necessary
  - Calcium acetate: no dose adjustment
  - Calcium citrate: no dose adjustment
  - Calcium gluconate: initiate with lower limit of the dosage
- Bisphoshonate:
  - Alendronate:
    - GFR>35 no dose adjustment
    - GFR<35 not recommended
    - Dialysis : not recommended

Osteoporosis & hypercalcemia treatment:

- Pamidronate: Renal impairment prior to therapy
  - GFR>30 : no dose adjustment
  - GFR< 30 : not recommended in breast cancer.
  - 90 mg or less in multiple myeloma
  - Hemodialysis: avoid use

Renal involvement during therapy: withhold therapy

- Zoledronic acid:
  - GFR>35 no dose adjustment
  - GFR<35 or AKI : contraindicated.

Osteoporosis & hypercalcemia treatment:

- Pamidronate:
  - Patients treated with pamidronate should have their kidney function closely monitored throughout their treatment with the medication. Clinicians should record serum creatinine before every infusion. In instances of renal deterioration, the patient should not receive the drug until creatinine rises to within 10% of the patient's baseline level. Electrolyte disturbances can also occur with the drug, and thus magnesium, potassium, phosphorus, calcium, and vitamin D levels should be monitored and corrected if necessary. Patients should also receive monitoring for albuminuria for 3 to 6 months after pamidronate infusion.

Osteoporosis & hypercalcemia treatment:

- Zoledronic acid:
  - The laboratory parameters such as renal function, vitamin D, calcium, magnesium, and phosphorus should be checked before each infusion. Electrolyte imbalances and vitamin D deficiency should be corrected before treatment is initiated. In patients receiving treatment for osteoporosis, periodic monitoring of bone mineral density should be completed to check for treatment response and effectiveness.

Osteoporosis & hypercalcemia treatment:

- RANKL Inh:
  - Denosumab: no dose adjustment
  - Belimumab: no dose adjustment
  - Anifrolumab: no dose adjustment

Osteoporosis & hypercalcemia treatment:

- Denosumab:
  - Within the first few weeks of treatment, monitoring of serum creatinine, calcium, phosphorus, and magnesium is recommended. Monitor for signs and symptoms of hypocalcemia and hypercalcemia upon discontinuation of denosumab.
  - A dental exam is recommended if osteonecrosis of the jaw is suspected. The bone mineral density evaluation should occur between 1 to 2 years after initiating treatment. The recommendation is for periodic monitoring of vitamin D and serum calcium throughout treatment.