ILD Collaborative

Project ECHO

A Guide to Starting and Monitoring Immunosuppression

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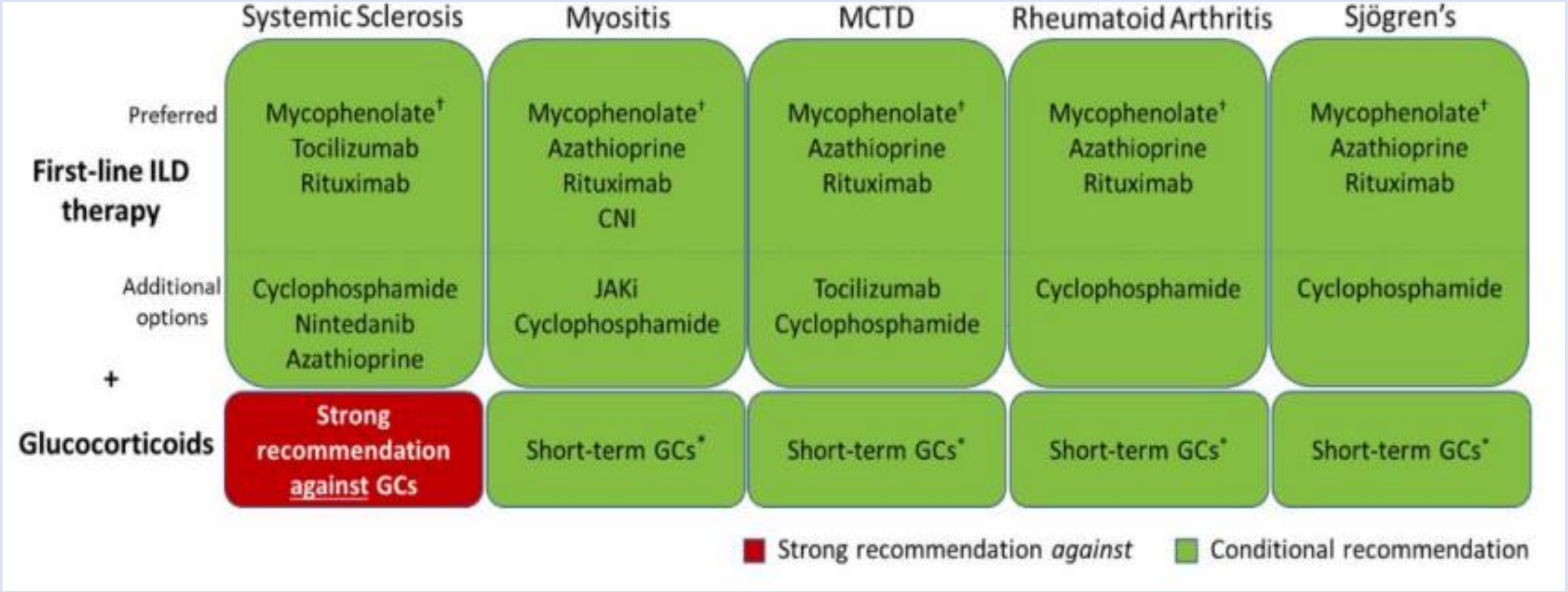
Disclosures

- PI for **Efficacy and Safety of Intravenous Efzofitimod in Patients with Pulmonary Sarcoidosis**
- Sponsor: aTyr Pharma, Inc
- Research Funds
- Study closed June 2025

Intent and Overview

- Gain comfort and experience using drugs traditionally prescribed by rheumatology
- Side effects, common and unusual
- Drug monitoring
- Indications to hold drug therapy
- Preventive health: vaccination guidelines on IS

Recommendations for Management of SARD-ILD: First-line ILD Treatment



Arthritis Care Res (Hoboken) 2024 Aug;76(8):1051-1069

Mycophenolate

- Postmarketing cases of hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with CELLCEPT (new Sept 2025)
- Increased risk of developing lymphomas and other malignancies, particularly of the skin
- Gastrointestinal bleeding requiring hospitalization, ulceration and perforations were observed in clinical trials
- Acute inflammatory syndrome (AIS): a paradoxical pro-inflammatory reaction characterized by fever, arthralgias, arthritis, muscle pain and elevated ESR and CRP, without evidence of infection or underlying disease recurrence. Symptoms occur within weeks to months of initiation of treatment or a dose increase. After discontinuation, improvement of symptoms and inflammatory markers are usually observed within 24 to 48 hours

Mycophenolate and PML

- Progressive Multifocal Leukencephalopathy is sometimes fatal and commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia
- FDA Adverse Event Reporting System (AERS) database review (2011):19 confirmed cases of PML in patients with SARD: 5 confirmed cases of PML in MMF treated patients had earlier received treatment with cyclophosphamide. These data indicate no clear signal of excess risk with mycophenolate mofetil above that seen with other non-biologic immunosuppressive agents, such as cyclophosphamide or azathioprine

Mycophenolate

- Drugs that may interfere with systemic exposure and reduce CELLCEPT efficacy: antacids with magnesium or aluminum hydroxide, proton pump inhibitors, telmisartan, calcium-free phosphate binders
- Drugs that Interfere with Enterohepatic Recirculation may reduce CELLCEPT efficacy: Cyclosporine A, trimethoprim/sulfamethoxazole, bile acid sequestrants (cholestyramine), rifampin, aminoglycosides, cephalosporins, fluoroquinolones and penicillins

Mycophenolate Safety Labs

- **Consider monitoring with complete blood counts weekly for the first month, twice monthly for the second and third months, and monthly for the remainder of the first year**
- If neutropenia develops (ANC <1300) stop or dose reduce (FDA)
- In clinical practice, a count of **less than 1,500 cells/mm³ (ANC) or less than 3,000 cells/mm³ (WBC)** should trigger some action

Mycophenolate

Marrow suppression, hepatotoxicity; black box warning regarding pregnancy	Mycophenolate mofetil: starting at 500 mg PO twice daily and gradually increasing to a therapeutic dose of 1,000–1,500 mg twice daily Mycophenolic acid: starting at 360 mg PO twice daily and gradually increasing to a therapeutic dose of 720–1,080 mg twice daily	CBC with differential and CMP at baseline, 2–3 weeks after starting and 2–3 weeks after any dose increase, and every 3 months once on a stable dose; full body skin examination, preferably by a dermatologist, annually

Arthritis & Rheumatology Vol. 76, No. 8, August 2024, pp 1182–1200

Frequency of Monitoring

Table 6. Recommendations for optimal followup laboratory monitoring intervals for complete blood count, liver transaminase levels, and serum creatinine levels for rheumatoid arthritis patients receiving nonbiologic disease-modifying antirheumatic drugs*

Therapeutic agents†	Monitoring interval based on duration of therapy		
	<3 months	3–6 months	>6 months
Hydroxychloroquine	None after baseline	None	None
Leflunomide	2–4 weeks	8–12 weeks	12 weeks
Methotrexate	2–4 weeks	8–12 weeks	12 weeks
Minocycline	None after baseline	None	None
Sulfasalazine	2–4 weeks	8–12 weeks	12 weeks

* More frequent monitoring is recommended within the first 3 months of therapy or after increasing the dose, and the outer bound of the monitoring interval is recommended beyond 6 months of therapy.
† Listed alphabetically.

Arthritis & Rheumatism (Arthritis Care and Research) Vol 59 (6) June 15 2008, pp 762-784

Rituximab

Medication	Notable toxicities	Starting doses and frequency	Monitoring
Rituximab	Cytopenias, infection, hepatitis B reactivation; black box warning for PML	1 g IV every 2 weeks for 2 doses; may be repeated every 24 weeks as needed	Hepatitis B virus infection, hepatitis C virus infection, and latent TB screening before initiation; CBC with differential at baseline and at 2- to 4-month intervals; monitor for infusion reactions

- To treat vasculitis, a smaller dose is given once a week for four weeks in a row
- Prophylactic antiviral therapy is strongly recommended over frequent monitoring of viral load and liver enzymes alone for patients initiating rituximab who are hepatitis B core antibody positive
- In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different bDMARD or tsDMARD
- Rituximab is conditionally recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity

Calcineurin Inhibitors

- Increasing use for myositis (esp MDA5 related)
- ACR guidelines 2023 conditionally recommend CNIs as a first-line ILD treatment option for people with IIM-ILD
- Variably absorbed in GI tract
- Highly lipophilic, binds to plasma proteins
- Primarily metabolized by Cytochrome P450 enzymes leading to a lot of drug-drug interactions which include those with calcium channel blockers (CCBs), azole antifungals, macrolide antibiotics, protease inhibitors, amiodarone, and certain selective serotonin reuptake inhibitors (SSRIs)

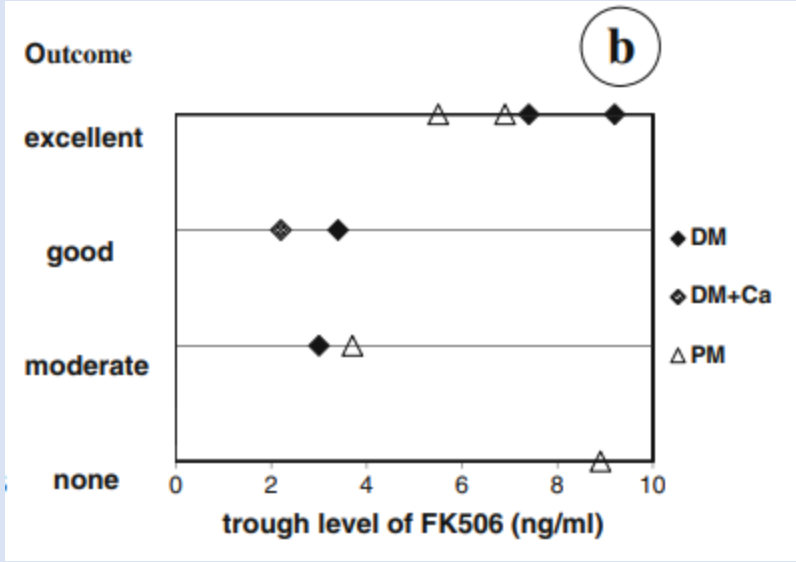
Tacrolimus

Toxicity Category	Manifestations	Mechanism and Risk Factors	Clinical Management
Nephrotoxicity	Increased serum creatinine, epithelial vacuolization, vasospasm, and interstitial fibrosis [48]	Calcineurin inhibition; high prevalence of FKBP12 in the kidney; associated with high-dose tacrolimus (>20 ng/mL) and CYP3A5 non-expressor genotype [48,50]	Reduce tacrolimus dose; monitor renal function; avoid nephrotoxic co-medications [49]
Neurotoxicity	Altered consciousness, tremors, headaches, posterior reversible encephalopathy syndrome (PRES), optic neuropathy, and psychosis [51–54]	Calcineurin inhibition affecting the CNS; optic neuropathy linked to structural changes in optic pathways [54]	Discontinue or reduce tacrolimus dose; symptoms like PRES and optic neuropathy are reversible with early intervention [55,57]
Cardiotoxicity	Hypertension, myocardial hypertrophy, QT prolongation, Torsade de Pointes, and arrhythmias (supraventricular and bradyarrhythmias) [60–67]	Vascular effects of calcineurin inhibition; electrolyte imbalances; grapefruit juice interaction increasing drug levels [66,67]	Monitor blood pressure, electrolytes, and ECG; avoid grapefruit products; consider alternatives in high-risk patients [66,67]
Metabolic effects	Dyslipidemia (increased LDL, triglycerides, and decreased HDL), post-transplant diabetes mellitus, hypomagnesemia, hyponatremia, and hyperkalemia [68–70,72,74]	Dysregulation of lipid and glucose metabolisms; renal tubular dysfunction leading to electrolyte imbalances [74]	Monitor lipid profile, blood glucose, and electrolytes; manage dyslipidemia and diabetes mellitus with appropriate medications [69,71]

Tacrolimus

- No standard guidelines for myositis
- Trough level may influence outcomes
- All four patients with an excellent outcome had a trough level >5 ng/ml

Effects of tacrolimus on dermatomyositis and polymyositis: a prospective, open, non-randomized study of nine patients and a review of the literature
Clin Rheumatol (2012) 31:1493–1498



Tacrolimus

- Start at a dose of 1 mg twice daily titrated by 1–2 mg daily with the goal of at least seven days between dose adjustment until target trough levels were reached
- To limit toxicity, target 12-hour tacrolimus trough levels were 5–8 ng/mL, which is lower than that used in most post-transplant patients
- Others recommend aiming for a trough level of 6-10 ng/mL

Benefit of adjunctive tacrolimus in connective tissue disease interstitial lung disease
Pulm Pharmacol Ther. 2016 February ; 36: 46–52

Rotella K, Alvarez MR, Saperstein Y, Bhamra MS, Leon SZ, et al. (2018) Tacrolimus-Induced Remission in Drug Resistant Inflammatory Myopathy: A Case Series. Rheumatology (Sunnyvale) 8: 238. doi:10.4172/2161-1149.1000238

Tacrolimus

- No standard guidelines for myositis

Medication	Notable toxicities	Starting doses and frequency	Monitoring
Tacrolimus	Leukopenia, renal failure, neurotoxicity	Dosing: 0.075 mg/kg/day adjusted for the target whole-blood trough levels between 5 and 10 ng/mL[16]; some experts use a maximum trough level of 6 ng/mL	Trough tacrolimus level, CMP, magnesium, phosphorus monitored 1–2 times per week for the first month, monthly for 3 months, then every 2–3 months; monitor BP

2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases

Major adverse effects of methotrexate*

Bone marrow toxicity
Neutropenia (most common, usually reversible)
Thrombocytopenia (dose related, usually reversible)
Anemia (rare)
Hepatic toxicity
Cirrhosis & fibrosis
Pulmonary toxicity
Opportunistic infections
PCP, CMV, herpes zoster, fungal, mycobacterial, etc
Noninfectious conditions
Hypersensitivity pneumonitis
Organizing pneumonia (previously called bronchiolitis obliterans with organizing pneumonia or BOOP)
Acute lung injury (noncardiogenic pulmonary edema)
Pulmonary fibrosis
Asthma/hyperreactive airways disease
Pleuritis and/or pleural effusion
Miscellaneous
Oligospermia
Teratogenicity
Malignancy

CMV: cytomegalovirus; PCP: Pneumocystis pneumonia.

* Major adverse effects are defined as potentially life threatening (incidence <1%) or requiring withdrawal of treatment (incidence 3 to 15%).

- Studied only in RA, extrapolated to other diseases
- Screen for Hepatitis B and C, TB
- Baseline CBC, CMP
- CBC, CMP every 4-8 weeks for 3 mo and if stable every 8-12 wks for 6 mo, then every 12 weeks (ACR)
- **Withhold if wbc <3K or plts < 50; LFT > 2 times ULN**
- Contraindicated if myelodysplasia or lymphoproliferative disease in last 5 years
- Contraindicated for treated or untreated chronic Hep B & C, or creatinine clearance < 30 ml/min, pregnancy or breast feeding
- Hold one week before and one week after surgery
- Minor LFT abnormalities common, especially if obese
- Folic acid is preventative
- Risk increases with additional biologic agents or hepatotoxic agents (leflunomide, Azathioprine, sulfasalazine etc)
- Macrocytosis expected but if >110 hold drug
- No more than 2-3 drinks per week
- Consider liver biopsy if 6/12 tests in a year are abnormal

Arthritis & Rheumatism. 59(6):762-84, 2008 Jun 15
Arthritis Care & Research 64 (5): 625-639, 2012 May

Methotrexate

Therapeutic dose: 15-25 mg weekly oral or SC

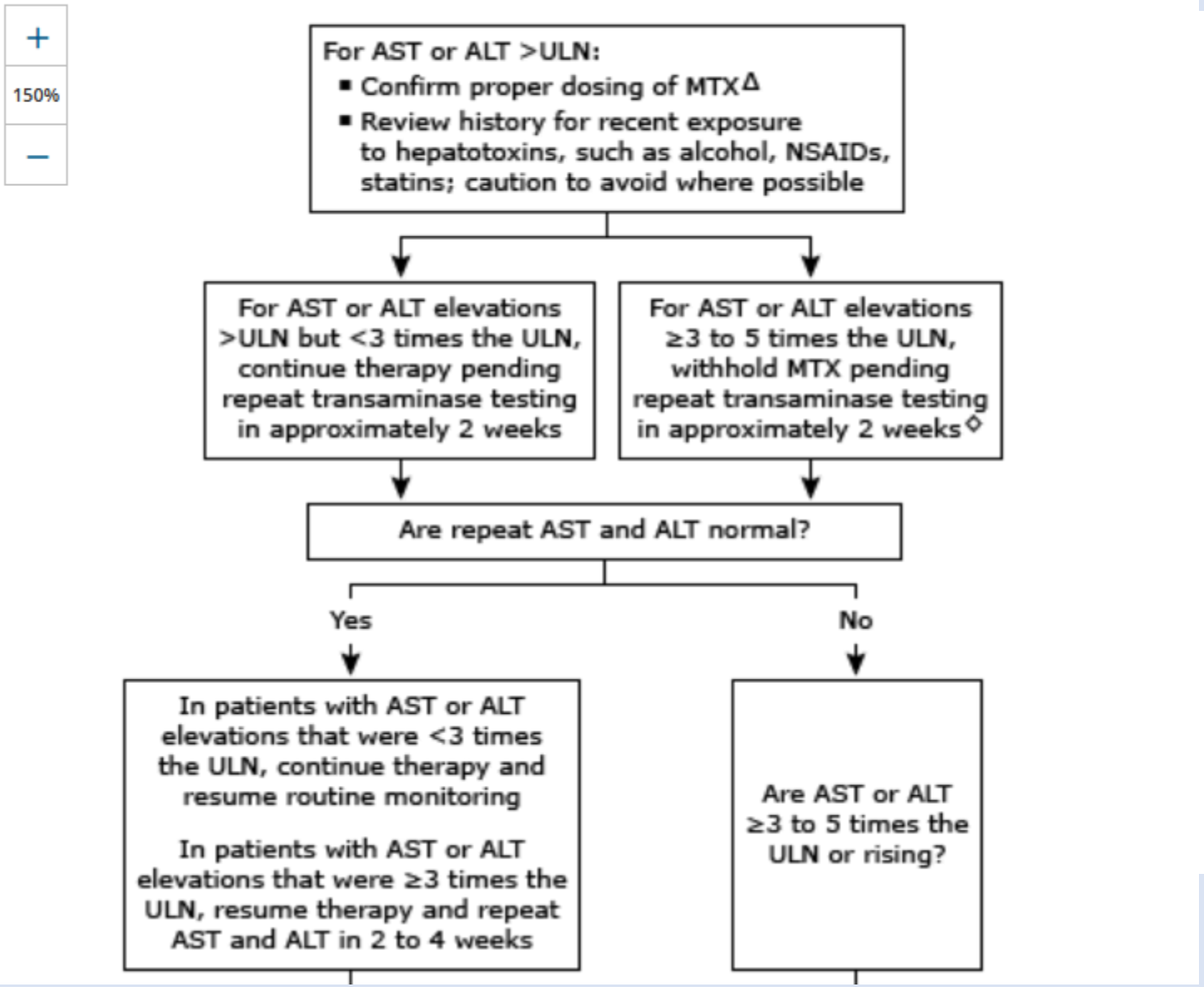
Monitoring: CBC and LFT, creatinine

GI side effects: Split doses, switch to SC

Folic acid 1 mg → 3-5 mg

Leucovorin

Initial management of abnormal liver function tests in patients on chronic low-dose MTX*



Methotrexate Pulmonary Toxicity

- MTX is contraindicated with RA pneumonitis or ILD of unknown cause (2008)
- Observational data suggest that methotrexate is not associated with progression of existing ILD (2023)

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Methotrexate Pulmonary Toxicity

- Case control study with discovery and replication populations: MTX use is not associated with an increased risk of RA-ILD in patients with RA; ILD was detected later in MTX-treated patients
- Multicenter prospective early RA inception cohort studies; the early RA study (ERAS) and the early RA network (ERAN):MTX treatment was not associated with an increased risk of RA-ILD diagnosis; evidence suggested that MTX may delay the onset of ILD (NS)
- According to the results from the 21 prospective studies, only 15 cases of MTX pneumonitis occurred among the 3463 patients with RA receiving MTX (0.43%) up to 36.5 months

Juge P-A, Lee JS, Lau J, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. Eur Respir J 2021; 57: 2000337
Kiely P, et al. BMJ Open 2019;9:e028466. doi:10.1136/bmjopen-2018-028466
Ann Rheum Dis 2009; 68: 1100–1104

Systemic Autoimmune Rheumatic Disease

- Conditional recommendation against methotrexate as first-line ILD treatment (2023)
- Methotrexate may be continued for extrapulmonary manifestations in patients with ILD
- Methotrexate should be stopped if there is concern for methotrexate pneumonitis, some would stop if ILD developed while on methotrexate

Nintedanib: Bleeding

- Nintedanib is a multi-targeted tyrosine kinase inhibitor
- Nintedanib blocks VEGF, which may lead to decreased platelet activity and leukocyte adhesion, which may increase the risk of bleeding and thrombosis
- Nintedanib blocks PDGF-α and PDGF- β which could affect thrombocyte production
  Although there is a potentially increased risk of bleeding due to VEGFR blockade, no increased incidence of cardiovascular complications or bleeding was observed based on the INPULSIS-1 and INPULSIS-2 trials

Nintedanib: Bleeding

- Most common: mild epistaxis
- There was no significant difference between the study and control groups in the major bleeding rate
- Patients with an inherited predisposition to bleeding and receiving full-dose anticoagulation were excluded
- Post marketing data: cases of major bleeding (both in anticoagulant and non-anticoagulant patients) from digestive system, respiratory and CNS bleeding
- Arterial thromboembolic events (myocardial infarction, stroke) occurred more frequently in the group using the drug (1.6% vs. 0.5% in INPULSIS)

Nintedanib: Bleeding

- Postmarketing data: over a period of approximately 1 year, bleeding adverse events occurred in less than 5% of 6758 nintedanib-treated patients, with less than 1% of patients having major bleeding events
- These data refer to both patients using and not using anticoagulation therapy
- German real-life study of 64 patients treated with nintedanib, 43.7% were on anticoagulation therapy: 21.8% received ASA, 10.9% VKA or DOACs and 4.7% combined therapy (ASA + OAC)
- During a median follow-up of 11 months (1 to 29 months), only 1 bleeding event was noted in the patient receiving combination therapy

Brunnemer, E.; Wälscher, J.; Tenenbaum, S.; Hausmanns, J.; Schulze, K.; Seiter, M.; Heussel, C.P.; Warth, A.; Herth, F.J.; Kreuter, M. Real-world experience with nintedanib in patients with idiopathic pulmonary fibrosis. Respiration 2018, 95, 301–309.

Nintedanib: Major Adverse Cardiovascular Events

- Post hoc analyses of pooled data from the TOMORROW and INPULSIS trials suggest that the incidence of MACE was similar between patients treated with nintedanib and placebo irrespective of cardiovascular risk at baseline
- The incidence of myocardial infarction was higher in the nintedanib group than in the placebo group among patients with higher cardiovascular risk, whereas the incidence rate of other IHD was lower in the nintedanib group than in the placebo group
- Overall, the incidence of myocardial infarction was similar in nintedanib-treated patients in the TOMORROW and INPULSIS trials as in epidemiological data from patients with IPF not treated with nintedanib

Noth I, Wijsenbeek M, Kolb M, et al. Cardiovascular safety of nintedanib in subgroups by cardiovascular risk at baseline in the TOMORROW and INPULSIS trials. Eur Respir J 2019; 54: 1801797

Nintedanib – Rare side effect

- Intestinal lymphangiectasia
- Fatigue, weight loss, abdominal pain, nausea, diarrhea
- Protein losing enteropathy with malabsorption symptoms
- Abd CT: diffuse thickening and submucosal fat attenuation of small bowel
- More common in younger patients on multitargeted TKIs
- Most commonly involves small bowel (71.4%) followed by large bowel (42.9%)
- Dilated lymphatic channels contain low density chylous fluid and look like fat attenuation
- Presence of submucosal fat on CT is associated with diarrhea and nausea
- Treatment cessation or dose reduction can improve symptoms and CT findings

Radiology 2022; 305:294

Nerandomilast

- Inhibitor of phosphodiesterase 4 (PDE4)
- CYP450 Enzymes: Nerandomilast is a CYP3A4 substrate
- Reduce Nerandomilast dosage to 9 mg twice daily when used concomitantly with strong CYP3A inhibitors (itraconazole)
- No dosage modification is recommended for Nerandomilast when used concomitantly with moderate or weak CYP3A inhibitors

Nerandomilast

- Nerandomilast trough concentrations at steady state decreased by approximately 50% following concomitant administration with pirfenidone in patients with IPF
- Recommended dosage of Nerandomilast is 18 mg twice daily when used concomitantly with pirfenidone
- Do not reduce dosage to 9 mg twice daily (no efficacy)

Methotrexate and Vaccines

Influenza, Pneumococcal and Hep B vaccination prior to initiation of therapy

Hold MTX for 1-2 weeks following:

- Flu vaccine
- Pneumococcal vaccine
- Tetanus
- Covid

Vaccinations

Medication management at the time of non-live attenuated vaccine administration

	Influenza vaccination	Other non-live attenuated vaccinations
Methotrexate	Hold methotrexate for 2 weeks *after* vaccination*	Continue methotrexate
Rituximab	Continue rituximab**	Time vaccination for when the next rituximab dose is due, and then hold rituximab for at least 2 weeks after vaccination
Immunosuppressive medications other than methotrexate and rituximab	Continue immunosuppressive medication	Continue immunosuppressive medication

*Hold only if disease activity allows. Non-rheumatology providers, e.g., general pediatricians and internists, are encouraged to give the influenza vaccination and then consult with the patient's rheumatology provider about holding methotrexate to avoid a missed vaccination opportunity.

**Give influenza vaccination on schedule. Delay any subsequent rituximab dosing for at least 2 weeks after influenza vaccination if disease activity allows.

= Conditional recommendation

2022 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases

Vaccinations

Whether to give or defer non-live attenuated vaccinations in patients taking glucocorticoids, regardless of disease activity

	Influenza vaccination	Other non-live attenuated vaccinations
Prednisone ≤ 10 mg daily*	Give	Give
Prednisone > 10 mg and < 20 mg*	Give	Give
Prednisone ≥ 20 mg daily*	Give	Defer**

*Or the equivalent dose of any other glucocorticoid formulation, or the equivalent pediatric dose
**Defer vaccination until glucocorticoids are tapered to the equivalent of prednisone < 20 mg daily

= Strong recommendation

= Conditional recommendation

2022 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases

Covid-19 Vaccine

Rituximab or other anti-CD20 B-cell depleting agents	Discuss the optimal timing of dosing and vaccination with the rheumatology provider before proceeding[‡]	Moderate
All other conventional and targeted immunomodulatory or immunosuppressive medications (e.g., JAKi, MMF) except those listed above[§]	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate

2022 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases