**Supplementary Material**

**Immunomodulation in Autoimmune Interstitial Lung Disease**

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**Supplementary Table 1.** Overview of immunomodulating agents used for ILD

| Agent | Regimens | Important reports [refs.] | Current treatment option in ILD | Routine monitoring/comment |
| --- | --- | --- | --- | --- |
| *Conventional sDMARDs* | | | | |
| Azathioprine | 2–2.5 mg/kg BW (max 150–200 mg) | Multicentric RCT: [9] (FAST)  Prospective open-label: [10, 110]  Retrospective studies: [11–15, 111] | SSc-ILD  CTD-ILD (RA; IIM)  Sarcoidosis | CBC, Cr (BL), LFTs  TPMT genotyping at BL |
| MTX | 10 mg once weekly p.o. or s.c. (max 15–20 mg) | Multicentric RCT [21]  Retrospective studies [15] | Sarcoidosis  RA-ILD | CBC, Cr, LFTs |
| Leflunomide | 20 mg once daily p.o.  (consider loading dose 100 mg on 3 consecutive days) | Retrospective studies [25–27] | Sarcoidosis  RA-ILD | Exclude latent TB  CBC, LFTs |
| Mycophenolate | Twice daily with target dose 2,000–3,000 mg/day | Multicentric RCTs: [30, 32, 112]  (SENSCIS; SLS II)  Retrospective studies: [12, 13,  33–36, 113] | SSc-ILD  CTD-ILD (IIM)  Fibrotic chronic hypersensitivity  pneumonitis | CBC, LFTs, Cr |
| CYC | ≤2 mg/kg BW p.o. daily  0.6 g/m2 BS i.v. every 4  weeks (6 cycles) | Multicentric RCTs: [30, 49, 114, 9] (SLS I, FAST, SLS II)  Prospective open label [69]  Retrospective studies [51–53] | SSc-ILD  Rapid-progressive IIM-ILD  AFOP  LIP in SjS-ILD  Rapid-progressive RA-ILD | CBC, urinalysis, Cr, electrolytes, leukocyte nadir, signs of cardiac toxicity, signs of hemorrhagic cystitis  Pneumocystis pneumonia prophylaxis |
| FK506 | Twice daily p.o.; target trough levels initially 5–20 μg/L, reduce to 5–8 μg/L | Retrospective studies [40–42] | Rapid-progressive IIM-ILD | CBC, LFTs, Cr, fasting glucose, lipids, electrolytes, trough levels Pneumocystis prophylaxis recommended when used with second DMARD |
| CSA | Twice daily p.o.; target trough level 100–200 μg/L | Prospective open label [46]  Retrospective studies [41–45] | Rapid-progressive IIM-ILD | CBC, LFTs, Cr, fasting glucose, lipids, electrolytes, trough levels  Pneumocystis prophylaxis recommended when used with second DMARD |
| *Targeted sDMARDs* | | | | |
| Tofacitinib | 5 mg twice daily per o.s. | Prospective open label [61]  Retrospective studies [60, 63] | Anti-MDA5-DM-ILD  (Cutaneous) sarcoidosis | CBC, lipids, LFTs |
| *bDMARDs* | | | | |
| Tocilizumab | 5 mg twice daily per o.s. | Prospective open label [61]  Retrospective studies [60, 63] | Anti-MDA5-DM-ILD  (Cutaneous) sarcoidosis | CBC, lipids, LFTs |
| Infliximab | 3 or 5 mg/kg BW i.v. at weeks 0, 2, and 6; then every 6–8 weeks | Multicentric RCTs: [95, 115]  Retrospective studies [97] | Sarcoidosis | Exclude latent TB and HBV  CBC, LFTs |
| Abatacept | 10 mg/kg BW s.c. every 4 weeks  125 mg s.c. weekly | Retrospective studies [104, 105] | RA-ILD  Sarcoidosis  Inflammatory myositisassociated ILD | Exclude latent TB and HBV  CBC, LFTs, Cr |
| RTX | 1,000 mg i.v. at day 0 and day 14 and at 6 months | Single-center RCT [66]  Prospective open label [67, 73, 77]  Retrospective studies [71, 72, 78–81, 83, 85] | CTD-ILD (SjS, RA-ILD, inflammatory myositisassociated ILD, SSc)  CVID-ILD [65]  Chronic hypersensitivity pneumonitis | Exclude HBV  CBC, Cr  Immunoglobulin levels (IgM, IgG, IgA)  Pneumocystis prophylaxis recommended |

BW, body weight; BS, body surface; CBC, complete blood count; CRP, C-reactive protein; CTD, connective tissue disease; FK506, tacrolimus; ILD, interstitial lung disease; IIM, idiopathic inflammatory myositis; LIP, lymphocytic interstitial pneumonia; LFTs, liver function tests; HBC, hepatitis B virus; TB, tuberculosis; MDA, melanoma differentiation-associated gene; p.o., per os; RA, rheumatoid arthritis; RCT, randomized controlled trial; s.c., subcutaneously; SLS, Scleroderma Lung Study; SjS, Sjögren’s syndrome; SSc, systemic sclerosis; TPMT, thiopurine S-methyl transferase; sDMARDs, synthetic diseasemodifying antirheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs; CYC, cyclophosphamide; CSA, cyclosporine A; RTX, rituximab; MTX, methotrexate.

**Supplementary Table 2.** Currently recruiting RCTs in ILD investigating immunomodulating agents

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| --- | --- | --- | --- | --- |
| Study acronym (NCT)/phase | Indication | Intervention | Estimated enrollment | Estimated completion |
| Scleroderma Lung Study III  (NCT03221257)/phase 2 | SSc-ILD (FVC ≤85%) | MMF (3,000 mg/d) + pirfenidone (3×801 mg/d) versus MMF + placebo | 150 | March 2022 |
| RECITAL (NCT01862926)/phase 2  (RTX), phase 3 (CYC) | CTD-ILD (SSc, IIM, MCTD) | RTX (1 g d1 + d15) versus CYC (600 mg/m2 6 doses 4 weekly) | 116 | November 2021 |
| EVER-ILD (NCT02990286)/phase 3 | IPAF, CTD-ILD, or NSIP | MMF (2 g/d) + RTX (1,000 mg d1 + d15) versus MMF + placebo | 122 | January 2021 |
| ATtackMy-ILD (NCT03215927)/phase 2 | IIM-associated ILD (antisynthetase syndrome) | Abatacept (125 mg weekly) versus placebo | 20 | May 2021 |

FVC, forced vital capacity; MCTD, mixed connective tissue disease; MMF, mycophenolate mofetil; RTX, rituximab; CYC, cyclophosphamide; SSc, systemic sclerosis; CTD, connective tissue disease; IIM, idiopathic inflammatory myositis; IPAF, interstitial pneumonia with autoimmune features; NSIP, nonspecific interstitial pneumonia.