Tocilizumab (ACTEMRA)
for Systemic Sclerosis Interstitial Lung Disease
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Tocilizumab is an interleukin-6 (IL-6) receptor antagonist.[1]
- It is the second drug and the first biologic approved for systemic sclerosis-associated interstitial lung disease (SSc-ILD).

Indication(s) Under Review in This Document

- Slowing the rate of decline in pulmonary function in adult patients with SSc-ILD.

Dosage Regimen Under Review

- 162 mg subcutaneously (SC) once every week.
- Dosage modifications are required for serious infections or abnormal liver enzymes (ALT / AST), neutrophil, or platelet count.

Dosage Forms Under Review

- Single-dose prefilled syringe 162 mg/0.9 mL
- Prefilled ACTPen autoinjector has not been studied in SSc-ILD, and intravenous (IV) administration is not approved for SSc-ILD.

Clinical Evidence Summary

Efficacy Considerations

- FocuSSced, a phase 3, placebo-controlled, randomized clinical trial (RCT),[2,3] was undertaken based on promising pulmonary results of faSScinate, a phase 2 placebo-controlled RCT.[4,5] In faSScinate, no significant treatment difference in the mRSS was shown at Week 24; however, clinically meaningful benefits in forced vital capacity (FVC) were observed. Of note, no statistical methods were used to control for multiplicity in the phase 2 trial.
- In focuSSced, potential benefit of tocilizumab in slowing the rate of decline in pulmonary function was shown in a subset of adults with early, active SSc-ILD who had an inflammatory component (not all patients with SSc-ILD have increased inflammatory markers).[6] Only a conclusion that "tocilizumab might preserve lung function" could be made based on secondary and exploratory efficacy results.[2]

- To control for multiplicity in focuSSced, a statistical hierarchical testing strategy was used. Because results showed no significant benefit in terms of the primary efficacy measure (modified Rodnan skin score [mRSS]), all subsequent tests (nominal p-values) on treatment differences, including FVC, were not considered to have achieved significance and could only be considered exploratory and inconclusive.[2]
- The FDA considered the possibility of a type 1 error but believed there was sufficient evidence to conclude that numerical FVC benefits were real and clinically meaningful.[7] The conclusion that the FVC benefits were not spurious was supported by the magnitude of FVC benefits, consistency both among FVC outcome measures and across studies, and reduction in lung fibrosis estimated by high-resolution computed tomography (HRCT). Also see Regulatory Considerations (page 6).
- No active-controlled RCTs were conducted.
- This monograph will focus on the phase 3 RCT.

FocuSSced Trial

Study Design

- FocuSSced was a 48-week, phase 3, multicenter, multinational, double-blind, placebo-controlled, 1:1 RCT conducted at 75 centers in 20 countries across Europe, North America, Latin America, and Japan. Patients were then eligible to continue in a 48-week open-label tocilizumab treatment phase. The double-blind and open-label phases evaluated tocilizumab at a dose of 162 mg SC once weekly.
- Inclusion criteria included diffuse cutaneous systemic sclerosis (SSc) of ≤5 years' duration (from onset of first non-Raynaud phenomenon manifestation), an mRSS of 10–35 units, and increased acute phase reactant(s) (C-reactive protein [CRP] ≥6 mg/L, erythrocyte sedimentation rate [ESR] ≥28 mm/h or platelet count ≥330 x 10^9/L).
    - To be eligible, patients also had to have active disease defined as at least one of the following: disease duration ≤18 months; mRSS increase of ≥3 units; involvement of one new body area and mRSS increase of ≥2 units; or involvement of two new body areas (each within the previous 6 months); and ≥1 tendon friction rub.
    - Patients were not required to have interstitial lung disease (ILD).
- Exclusion criteria included significant restrictive lung disease (percentage of predicted FVC [ppFVC] of ≤55%), significant impairment in lung diffusion (percentage of predicted diffusing capacity of the lungs for carbon monoxide [ppDLCO] ≤45%), World Health Organization (WHO) [functional] class 2 or higher pulmonary arterial hypertension or evidence of other moderately severe pulmonary disease, body weight >150 kg, current liver disease, and glomerular filtration rate <45 mL/min.
- Rescue immunomodulatory therapy (only one agent) could be added to study therapy from Week 16 for patients who experienced a decrease in ppFVC or from Week 24 for patients who had worsened skin thickening or other substantial SSc complications. However, cyclophosphamide was among the agents not permitted during the trial.
- Randomization used a permuted block method and was stratified by serum IL-6 levels (<10 or ≥10 pg/mL) to account for a previously observed association between lower IL-6 levels and better SSc skin outcomes.
- A thoracic radiologist identified patients with ILD post hoc based on HRCT findings and a diagnostic algorithm for SSc.

Efficacy Outcome Measures

- The primary efficacy measure was the change from baseline (CFB) in mRSS at Week 48. The total score for mRSS ranges from 0/No skin thickening to 51/Severe skin thickening.
- Pulmonary function including FVC at Week 48 was a key secondary efficacy outcome. FVC was measured using a centralized spirometry system.

- As reference, in the Scleroderma Lung Studies, a minimal clinically important change (MCIC) from baseline to 12 months was shown to range from 3.0% to 5.3% for ppFVC improvement and –3.0% to –3.3% for worsening.[8]

Patient Characteristics

- Of 343 patients screened, 212 (62%) met entry criteria. Of 212 patients randomized, 136 patients (64%; 40% of patients screened) had HRCT-confirmed SSc-ILD at baseline; this was the subgroup analyzed for effects on pulmonary function.
- Overall (N = 208 analyzed), mean age was 48.2 (± 12.4) years; 19% of patients were male, 83% white, and 12% Asian. Median disease duration was <2 years. Patients had moderate to severe skin involvement with mean mRSS of 20.4 and normal to mild impairment in lung function with ppFVC of 82.1 and ppDLCO (hemoglobin corrected) 75.6 and lung fibrosis identified on HRCT in 2%–17% of patients. Serum IL-6 concentrations were less than 10 pg/mL in 73% of patients.
- At least one previous medication for SSc was used in 66 tocilizumab patients (64%) and 63 placebo patients (59%).[7] Mycophenolate mofetil was previously used in 9% of patients in both treatment groups and cyclophosphamide was previously used in 8% and 11% of the tocilizumab and placebo groups, respectively.[7]

Results

- Immunomodulatory therapy was started in 9 (9%) of 104 patients on tocilizumab and 22 (21%) of 106 patients on placebo during the 48-week double-blind phase, with most patients (18/31, 58.1%) starting immunomodulators at or after Week 36.[2]
- Primary Efficacy Outcome. The treatment differences in CFB in skin thickness, as measured by mRSS, did not reach the level of statistical significance at Weeks 24 and 48 (Table 1).

Table 1 Selected efficacy results from focuSSced (mITT)

	Time	Tocilizumab		PBO			
Outcome	**(Wks)**	**N**	**Result**	**N**	**Result**	**Diff or HR (95% CI)**	**Q**
Primary outcome							
CFB in mRSS, LSM (95% CI)	24	104	–3.7 (–5.0, –2.4)	106	–3.1 (–4.3, –1.8)	Diff –0.6 (–2.3, 1.0)	H
	48	104	–6.1 (–7.7, –4.6)	106	–4.4 (–6.0, –2.9)	Diff –1.7 (–3.8, 0.3)	H
Key secondary outcomes							
aDFB of >10% in ppFVC,‡§ n (%)	48	104	13 (13)	106	25 (24)	HR 0.55 (0.3, 1.1)	L^{α}
CFB in ppFVC, %, LSM (95% CI)	48	104	–0.4 (NR)	104	–4.6 (NR)	**Diff 4.2 (2.0, 6.4)**	M^{β}
CFB in HAQ-DI (95% CI) n	48	103	–0.11 (–0.22, –0.01)	102	–0.06 (–0.16, 0.05)	Diff –0.05 (–0.19, 0.09)	$L^{\beta\delta}$
Treatment Failure,‡ n (%)	48	104	23 (22)	106	37 (35)	HR 0.6 (0.4, 1.1)	$L^{\beta\nu}$
Death,‡ n (%)	48	104	1 (1)	106	3 (3)	HR 0.37 (0.0–3.6)	$L^{\beta\nu}$
Exploratory outcomes							
aDFB of ≥10% in ppFVC, n (%)	48	93	5 (5.4)	91	15 (16.5)	NA	$VL^{\beta\varepsilon}$
CFB in FVC, mL, LSM	24	104	–13	104	–101	**Diff 88 (24, 152)**	M^{β}
	48	104	–24	104	–190	**Diff 167 (83, 250)**	M^{β}
CFB in oHRCT QLF-LM, median (95% CI) n	48	60	0.0 (–0.3, 0.2)	66	0.3 (0.0, 0.8)	**Diff –0.3 (–0.6, 0.0)**	$L^{\beta\delta}$
Outcomes analyzed post hoc							
CFB in oHRCT QLF-WL, median (95% CI) n	48	84	0.0 (–0.2, 0.1)	81	0.1 (0.0, 0.3)	**Diff –0.1 (–0.3, –0.05)**	$L^{\beta\delta}$
CFB in oHRCT QILD-WL, median (95% CI) n	48	84	–0.9 (–2.0, –0.2)	80	0.4 (–1.0, 2.0)	**Diff –1.3 (–2.8, –0.3)**	$L^{\beta\delta}$

Sources: 2,3,9

Bolded results indicate nominal p <0.05 (p-values were nominal because the primary outcome analysis was not significant).

aDFB, Absolute decrease from baseline; CFB, Change from baseline; H, High; HAQ-DI, Health assessment questionnaire disability index; HR, Hazard ratio; L, Low; LSM, Least square mean; M, Moderate; mITT, Modified intent to treat; mRSS, Modified Rosnan skin score; NA, Not assessed (exploratory measure without statistical comparison); oHRCT, Observed high-resolution CT; P2, Phase 2 faSScinate trial; P3, Phase 3 focuSSced double-blind phase; P3OLE, Phase 3 focuSSced open-label extension; Q, GRADE quality of evidence;. QILD-WL, Quantitative interstitial lung disease-whole lung. QLF-LM, Quantitative lung fibrosis-most affected lobe. QLF-WL, Quantitative lung fibrosis-whole lung; RR, Relative risk; VL, Very low.

† Treatment failure was defined as time from treatment start to death, decrease in ppFVC >10%, relative increase in mRSS >20% and ≥5 mRSS points, or occurrence of a predefined and adjudicated serious complication related to SSc.

‡ As a component of treatment failure; time to treatment failure was a secondary outcome.

§ Note that this measure uses greater than 10% decrease and differs from the similar exploratory measure that uses greater than or equal to 10% decrease.

α Downgraded for imprecision (<300 events; calculated CI for difference includes value of questionable clinical importance) and inconsistency (dissimilar results between outcomes that captured similar concepts: using a slightly different cutoff of >=10% as an exploratory outcome, the lower limit of CI for the difference exceeded 1.0). Calculated difference, 11.1 (0.63, 21.35).

β Downgraded for risk of bias related to multiple comparisons

δ Downgraded for imprecision (CI for the treatment difference includes 0 or value of questionable clinical importance).

γ Downgraded for imprecision (<300 events; CI includes zero or value of questionable clinical importance).

ε Downgraded for imprecision (<300 events) and inconsistency (dissimilar results between outcomes that captured similar concepts).

- Selected Key Secondary Outcomes
    - CFB in ppFVC at Week 48: Exploratory statistical testing of the treatment difference (4.2 [95% CI 2.0–6.4]) for the least square mean (LSM) CFB in ppFVC at Week 48 resulted in a nominal p-value of 0.0002.
    - The CFB in ppFVC indicated worsening in the tocilizumab (–0.4) and placebo groups (–4.6); however, the CFB was less than the MCIC (was not clinically important) for worsening of –3.0% to –3.3% with tocilizumab, whereas the CFB exceeded the MCIC (was clinically important) in the placebo group.
    - The Kaplan-Meier analysis of time to treatment failure at Week 48, adjusted for baseline IL-6 strata (<10 pg/mL, ≥10 pg/mL), resulted in a HR of 0.6 (95% CI 0.4, 1.1) and a nominal p-value of 0.08.
- Components of treatment failure at Week 48 in focuSSced
    - Nonsignificant nominal p-values (p ≥0.05) were obtained for rates of treatment failure, ppFVC >10%, mRSS increase >20% and ≥5%, SSc-related complication, deaths, treatment failure excluding decline in ppFVC, and treatment failure excluding increase in mRSS.
- FACIT-fatigue scores at Week 48 in focuSSced were 5.1 vs 2.6 in the tocilizumab vs placebo groups, respectively (nominal p = 0.04).
- Nominal p-values of ≥0.05 were obtained for other secondary efficacy measures at Week 48, including disability (HAQ-DI), patient global assessment, and investigator global assessment.
- Exploratory Outcome Measures
    - Formal statistical comparisons were not done for exploratory measures.
    - The 95% CIs overlapped between the active and placebo groups for observed ppDLCO, Scleroderma Health Assessment Questionnaire (SHAQ) VAS and the St. George's Respiratory Questionnaire (SRGQ).
    - The percentage of patients with ≥15% decrease in ppDLCO was similar between the tocilizumab and placebo groups (9% vs 10%, respectively).
    - The American College of Rheumatology provisional Composite Response Index in Systemic Sclerosis (ACR-CRISS) predicted a probability of CFB in overall health status of ≥0.6 in 53 (51%) of 104 tocilizumab-treated patients and 39 (37%) of 106 placebo patients, with a difference of 13.9 percentage points (95% CI 1.0–26.8; nominal p = 0.04). The ACR-CRISS is a composite global patient-reported outcome measure that incorporates the HAQ-DI, patient and physician global assessments of SSc-related health, and FVC.

- Subgroup Analyses
    - In the subgroup of patients with SSc-ILD, CFB in ppFVC and CFB in FVC were numerically lower in the tocilizumab group and nominal p-values were <0.05 (Table 2).

Table 2 Lung Outcomes in SSc-ILD Subgroup

	Time	Tocilizumab		PBO			
Outcome	**(Wks)**	**n**	**Result**	**n**	**Result**	**Difference (95% CL)**	**Q**
CFB in ppFVC, %, LSM	48	68	0.1	66	–6.4	**6.5 (3.4, 9.5)**	L[α]
aDFB of ≥10% in ppFVC, n (%)	48	59	5 (9)	56	14 (25)	NA	L[β]
Improvement by ≥0% in ppFVC, n (%)	48	59	27 (46)	56	13 (23)	NA	L[β]
CFB in FVC, mL, LSM	24	68	–15	66	–133	**118 (31, 205)**	L[α]
	48	68	–14	66	–255	**241 (124, 358)**	L[α]
CFB in oHRCT QLF-LM, mean (95% CI)	48	35	–2.2 (–4.5, 0.2)	36	1.9 (0.6, 3.2)	—	L[δ]
Outcomes analyzed post hoc							
CFB in oHRCT QLF-WL, mean (95% CI)	48	54	–0.6 (–1.4, 0.2)	48	0.7 (0.3, 1.2)	—	L[δ]
CFB in oHRCT QILD-WL, mean (95% CI)	48	54	–2.1 (–4.0, –0.2)	47	1.5 (–0.3, 3.4)	—	L[δ]

Bolded results indicate nominal p <0.05 (p-values are nominal because the primary outcome analysis was not significant).
aDFB, Absolute decrease from baseline; NA, Not applicable (exploratory outcome); oHRCT, Observed high resolution computed tomography; QILD-WL, Quantitative interstitial lung disease-whole lung; QLF-LM, Quantitative lung fibrosis-most affected lobe; QLF-WL, Quantitative lung fibrosis-whole lung
[α] Double downgraded for risk of bias (no stratified randomization in SSc-ILD subgroup, multiplicity) and imprecision (small N).
[β] Double downgraded for risk of bias (no stratified randomization in SSc-ILD subgroup, multiplicity) and imprecision (<300 events).
[δ] Double downgraded for risk of bias (no stratified randomization in SSc-ILD subgroup, multiplicity) and imprecision (small N; CI for mean includes values of questionable clinical importance).

    - In the subgroup without ILD, there was no significant treatment difference in the CFB in ppFVC at Week 48.
    - Therefore, the pulmonary benefits observed in the overall population were primarily driven by the response in the ILD subgroup.[7]
- Post-hoc Analyses
    - Tocilizumab reduced progression of ppFVC independent of baseline extent of quantitative radiographic ILD and fibrosis.[3]
- Sensitivity Analyses
    - Using different assumptions about missing data for ppFVC, sensitivity analyses did not show convincing robustness of the nominally significant results for the overall (intent-to-treat) population but did show robustness in the ILD subgroup.[7]
- Duration of an Adequate Trial
    - The maximal CFB in ppFVC during tocilizumab therapy seemed to occur around Week 16 in the overall population.
    - In the ILD subgroup, near-maximal CFB in ppFVC occurred at Week 16, and maximal CFB occurred at Week 36.
    - The duration of an adequate trial denotes the earliest time to determine adequacy of tocilizumab therapy and whether the treatment plan needs to be modified to improve effectiveness. However, it is difficult to set an adequate trial duration when the end point is negative (i.e., no or little worsening of ppFVC) as opposed to positive (e.g., achieving a certain ppFVC threshold).
- Open-label Extension (Week 48 to Week 96)

- The median change from Week 48 to Week 96 in ppFVC in patients who switched from placebo to tocilizumab was 0.27%.[7] This small magnitude of change was consistent with the negligible change (–0.60%) observed on tocilizumab and contrasted with the 3.9% decrease seen on placebo during the first 48 weeks of the trial.[7] Mean changes were not reported.

Network Meta-analyses (Indirect Comparative Efficacy)

- No meta-analysis including tocilizumab for SSc-ILD was found.

Safety Considerations

- **Boxed Warnings, Contraindications, Other Warnings / Precautions**: See prescribing information.
- **Safety in focuSSced Trial**: The safety profile of tocilizumab up to Week 48 in the focuSSced trial was consistent with the known safety profile of tocilizumab.
  - **Deaths**: See Table 1.
  - **Serious Adverse Events** (tocilizumab vs placebo, respectively): 13% vs 17% of patients. The tocilizumab group had numerically lower rates of serious infections (2% vs 7% of patients) and more cases of serious cardiac events (6 patients vs 2 patients).
  - **Withdrawals Due to Adverse Events** (tocilizumab vs placebo, respectively): 2% vs 3% of patients.
- **Safety Concerns Reported in Case Reports**: Paradoxical acute pulmonary deterioration (hypoxemia, extensive ground-glass opacities on HRCT) occurred in a woman with a usual interstitial pneumonia (UIP) pattern of SSc-ILD after being switched from mycophenolate mofetil to tocilizumab.[10] The pulmonary event started after the ninth dose of tocilizumab and resolved after discontinuing tocilizumab and restarting mycophenolate mofetil. The authors advised caution when tocilizumab is used in patients with the UIP phenotype of SSc-ILD.

Other Considerations

Regulatory Considerations

- mRSS captures only one component of SSc disease and is confounded by its highly variable trajectories over time (>50% of patients with diffuse cutaneous SSc spontaneously improve over the first 3–5 years after onset of disease).[7] The mRSS may be an inadequate measure for capturing relevant changes over time and differentiating active treatment from placebo.[7]
- At the time that the tocilizumab clinical trials were being prepared, FVC had not yet gained agreement as a meaningful outcome measure, so mRSS remained the primary efficacy measure.[7] The regulatory requirements regarding the use of FVC in fibrosing lung diseases subsequently evolved (a decrease in FVC of ≥10% was shown to be associated with increased risk of mortality in idiopathic pulmonary fibrosis[7]) and the FVC became the focus of the FDA review, considering the limitations of using mRSS.
- Based on a very low estimated probability of 0.0125 (1 in 80) for observing statistically significant results on at least one of the outcome measures in both the phase 2 and phase 3 RCTs, the FDA believed that it was unlikely that the favorable FVC results in both trials were false positives.[7] The FDA concluded that the "unique regulatory history and context of use mitigate the concerns about the impact of multiplicity in studies without evidence of statistical effects on the primary endpoint, and…leads to confidence in the evidence of effectiveness."[7]

No Recommendations for Weight-based Dosing

- Higher body weight, particularly weight >100 kg, is associated with decreased systemic exposure to tocilizumab.[7]

- A flat dose of 162 mg of tocilizumab is recommended for SSc-ILD, and the phase 3 RCT excluded patients weighing >150 kg.

Other Therapeutic Options

Overview of Treatment Alternatives

- Treatment alternatives for SSc-ILD are limited and noncurative, and the optimal treatment and treatment approach (e.g., step-up, add-on therapy vs upfront combination therapy) are unknown.
- ILD more commonly manifests itself at the time of or soon after the diagnosis of SSc but can present years later.[11] In general, patients should be started on immunosuppressive therapy early when the disease is active, particularly in patients with significant progression since damage is irreversible once it occurs.[12] The 2017 European Dermatology Forum (EDF) S1 guideline on the diagnosis and management of sclerosing diseases of the skin defines significant progression as a reduction in FVC of >5% in 6 months or >10% in 1 year or in DLCO of >15% in 1 year.[12] Volkmann and Tashkin (2016) have suggested considering treatment in patients with SSc-ILD if there was a clinically significant and sustained decline in FVC (decrease by >10%) or in DLCO (decrease by >15%) in the absence of pulmonary hypertension, progression of ILD on HRCT, or development of SSc-ILD symptoms not explained by other causes.[13]
- The EDF S1 guideline did not make any recommendations for treatment sequencing for SSc-ILD but did mention that some experts recommend following the initial 6 or 12 pulses of cyclophosphamide therapy with azathioprine or mycophenolate mofetil to prolong immunosuppression.[12] The S1 guideline did not include the 2016 Scleroderma Lung Study II, which showed that mycophenolate mofetil was as effective as and safer than cyclophosphamide in SSc-ILD.
- In other expert consensus recommendations, mycophenolate mofetil is suggested as first-line therapy for both induction and maintenance.[14, 15] Cyclophosphamide is suggested second-line and rituximab third-line for induction therapy.[15] For maintenance therapy, azathioprine is suggested as second-line and cyclophosphamide is suggested third-line therapy.[15]
- Expert opinion suggests tocilizumab as an alternative to mycophenolate mofetil as initial therapy.[19]
- Autologous hematopoietic stem cell transplantation (HSCT) has also been shown to be effective for both skin and lung fibrosis in two large RCTs.[16,17] Because of potential treatment-related mortality, HSCT has been suggested for patients who fail standard therapy or have life-threatening disease[6] or selected patients with rapidly progressive SSc at risk of organ failure.[18]
- Alternative drug treatments for SSc-ILD are summarized in Table 3.

Table 3 Pharmacologic Treatment Alternatives for SSc-ILD

Drug / Dosage	Formulary	Place in Therapy in SSc†	Safety Considerations	Other Considerations
Targeted IL-6 Inhibitor				
Tocilizumab 162 mg SC once weekly Dosage modifications for ALT/AST, ANC, and PLT. No renal dosage modifications.	NonF (inj) w/CFU in Rheumatologic Diseases	For ILD. No significant benefit for skin fibrosis. Induction: 2nd-line (alternative to MMF as initial tx)[19] Maintenance: 2nd-line (alternative to MMF)[19]	Boxed Warning: Serious infections Tuberculosis, herpes zoster reactivation, neutropenia, thrombocytopenia, hyperlipidemia, liver injury, GI perforation. Rare demyelinating CNS disease.	Evidence obtained in post hoc subgroup of patients with diffuse cutaneous SSc-ILD with increased inflammatory markers. No significant benefit in function / QOL and survival. Obesity may reduce drug exposure but no recommendations for dosage modification.

Drug / Dosage	Formulary	Place in Therapy in SSc†	Safety Considerations	Other Considerations
				Lack of evidence to inform safety / efficacy of use in combination with MMF or CyP.
Inosine monophosphate dehydrogenase inhibitor				
Mycophenolate Mofetil (MMF) 500 to 1500 mg PO twice daily. Reduce dose in ESRD. Separate doses of MMF and PPIs, antacids, and mineral supplements by ≥2 h (reduce absorption of MMF).	Yes (cap, inj, tab, EC tab) Susp is NonF	For skin and ILD (off-label use). Induction: 1st-line[15] Maintenance: 1st-line[15]	Well tolerated. Better tolerated and fewer SAEs and tx failures than PO CyP.[20] GI effects, myelosuppression, infections.	In the SLS II study involving patients with symptomatic, moderate SSc-ILD, MMF had nonsignificantly fewer deaths vs PO CyP and was similar to PO CyP in ppFVC, other PFTs, HRCT, dyspnea / cough / QOL, and skin fibrosis over 24 mos.[20] A PC RCT (MYILD) in 41 patients w/mild SSc-ILD showed significant benefit in mRSS and no significant benefit in FVC and DLCO at 6 mos.[21]
Regulatory T cell inhibitor (low doses)				
Cyclophosphamide (CyP) IV Pulses: 500–600 mg/m^2 BSA every 2–4 wks for up to 6 doses. If used for maintenance, 500 mg/m^2 IV every 12 wks for 18 mos. Oral: 1–2 mg/kg/d PO Modify dose for age >70 y, obesity, and CrCl.	Yes (cap, inj) Tab is NonF	For skin and ILD (off-label use). Induction: 2nd-line[15] Maintenance: 3rd-line[15]	IV CyP given monthly seems to be safer than PO CyPP.[22] Hemorrhagic cystitis, myelosuppression. Contraindications include infection, neutropenia. Avoid in pts w/history of CyP hemorrhagic cystitis.	In SLS I (patients with symptomatic, moderate SSc-ILD), PO CyP produced a modest (2.53%) absolute improvement in ppFVC.[23] Improved dyspnea, QOL, skin thickness, and lung fibrosis.[24,25] However, a meta-analysis did not confirm PFT benefits.[26] Loses tx effect 1–2 y after discontinuation. However, cumulative toxicity limits its long-term use.
Tyrosine kinase inhibitor / Antifibrotic				
Nintedanib 150 mg PO every 12 h Reduce dose in mild hepatic impairment.	NonF (cap) w/CFU CFU: Progressive SSc-ILD – 2nd-line after MMF or CyPP	For ILD. No benefit for skin fibrosis. Induction / Maintenance: Add-on tx for progression despite MMF or CyP.[19]	Use not recommended in moderate or severe hepatic impairment. Hepatic injury, arterial thromboembolism, increased risk of bleeding. Not immunosuppressive. Smoking decreases nintedanib exposure and should be avoided before and during therapy. Diarrhea in 76% of pts.[27]	Decreased the rate of decline in FVC over 52 wks in pts w/established limited or diffuse SSc and associated ILD and no pulmonary HTN.[28] No effect on QOL / patient-reported outcomes and survival. Greater FVC benefit with concomitant MMF.[28] No evidence to inform appropriateness of monotherapy.
Purine synthesis inhibitor				
Azathioprine (AZP) 2.5 mg/kg PO once daily	Yes (50-mg tab, inj)	Off-label Maintenance: 2nd-line[15]	Long-term use associated with malignancy.	No PC RCTs. NSD between CyP x 1 y then AZP x 1 y vs MMF x 2 y.[22]

Drug / Dosage	Formulary	Place in Therapy in SSc†	Safety Considerations	Other Considerations
	AZASAN equivalents (75- and 100-mg tabs) are NonF		GI, liver, and hematologic toxicities. Myelotoxicity in pts with TPMT or NUDT15 deficiency.	Ineffective for skin and lung function in CyP vs AZP RCT.[29]
B-lymphocyte CD20 inhibitor				
Rituximab-pvvr **Rituximab** **Rituximab-abbs** Various doses studied; effective dose not established. E.g., 1000 mg IV every 2 wks for 2 doses (1 cycle); repeat cycle every 6 mos.	Yes (inj) NonF NonF	Might improve skin and ILD (off-label use). Induction: 3rd-line[15]	Boxed warnings for infusion reactions, mucocutaneous reactions, HBV reactivation, and PML. Herpes zoster	Lacks rigorous trials; potential benefit has been suggested in a small proof-of-principle study,[30] a nested case-control study (EUSTAR),[31] case series,[32,33,34,35] and meta-analysis.[36]
General immunosuppressant, primarily T-lymphocytes				
Prednisone or Other Glucocorticoid ≤20 mg PO once daily	Yes	Induction: No consensus[15] Adjuvant to CyP: Controversial. No role in tx of SSc fibrosis.[12]	Glucocorticoid class adverse events, particularly with longer term use. Doses >15 mg have been associated with increased risk of SSc renal crisis.[12]	Most experts endorsed using ≤20 mg/d for ≤6 mos.[15]

Sources: 15,19,37

† Place in therapy for induction and maintenance are based on expert consensus or UpToDate authors' opinions.

AD, Adverse event; ANC, Absolute neutrophil count; CyP, Cyclophosphamide; dcSSc, Diffuse cutaneous systemic sclerosis; DLCO, Diffusing capacity of the lungs for carbon monoxide; ESRD, End-stage renal disease; HBV, Hepatitis B virus; HRCT, High resolution computed tomography (quantification of fibrosis / ILD); ILD, Interstitial lung disease; lcSSc, Limited cutaneous systemic sclerosis; MMF, Mycophenolate mofetil; mRSS, Modified Rodnan skin score; NonF, Nonformulary; NSD, No significant difference; NUDT15, Nudix hydrolase 15; PBO, Placebo; PC, Placebo-controlled; PFT, Pulmonary function tests (e.g., DLCO% predicted, DLCO/VA% predicted); PLT, Platelet count; PML, Progressive multifocal leukoencephalopathy; SAE, Serious adverse event; SLS, Scleroderma Lung Study; TDI, Transitional dyspnea index; TPMT, thiopurine S-methyltransferase

Differences in Study Populations Among Studies of Tocilizumab and Other Agents

- Tocilizumab was studied in a different subset of SSc patients than mycophenolate mofetil, cyclophosphamide, and nintedanib (Table 3).

Table 4 Comparison of Drug Study Populations

Characteristic	Tocilizumab	Mycophenolate Mofetil	Cyclo-phosphamide	Nintedanib
Trial(s)	focuSSced	SLS II	SLS I and SLS II	SENSCIS
Type of SSc	Diffuse	Limited or diffuse	Limited or diffuse	Limited or diffuse
ILD Required	No	Yes	Yes	Yes
Criterion for duration of SSc (y)†	≤5	≤7	≤7	≤7
Mean duration of SSc (y)†	1.9	2.6	3.2 and 2.5	3.4 (median)
Required elevated acute phase reactants	Yes	No	No	No
Excluded clinically significant or treated PAH	No‡	Yes§	Yes§	Yes€
Criterion for ppFVC at BL	>55%	45% to 85%	45% to 85%	≥40%

Mean baseline ppFVC	82%	66%	68% and 66%	72%
Concomitant mycophenolate	5%	NA	Not reported	48.4%
Required absence of smoking in past 6 mos	No	Yes	Yes	No[¥]
Basis of criteria for active / progressive disease	SSc	ILD	ILD	ILD

BL, Baseline; PAH, Pulmonary arterial hypertension; SLS, Scleroderma Lung Study

† From onset of first non-Raynaud phenomenon manifestation

‡ Specifically excluded WHO [functional] class 2 and higher. Allowed WHO class 1 only, regardless of whether the patient received treatment for PAH.

§ Excluded clinically significant pulmonary hypertension requiring drug therapy.

€ Excluded clinically significant pulmonary hypertension defined as previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterization with a cardiac index of ≤2 L/min/m^2 or pulmonary hypertension that led to parenteral therapy with epoprostenol or treprostinil.

¥ Discontinuation of smoking is recommended prior to initiating nintedanib therapy because tobacco can decrease serum concentrations of nintedanib.

- Tocilizumab was evaluated in patients at an earlier SSc stage with a mean disease duration from the onset of first non-Raynaud phenomenon manifestation of 1.9 years as compared with 2.5–3.4 years for mycophenolate mofetil, cyclophosphamide, and nintedanib. The faSScinate and focuSSced trials intended to evaluate tocilizumab in patients with very early disease based on previous studies suggesting that IL-6 may be pathogenically important in a relatively early phase of SSc, particularly those with lung lesions.[38]
- IL-6 produces acute phase proteins; therefore, presence of acute phase reactants was a unique entry criterion in the selection of patients for the tocilizumab clinical trials. Notably, this requirement made the tocilizumab study population a subset of the SSc population, since not all patients have elevated inflammatory markers.

Projected Place in Therapy

- **Epidemiology and Prevalence of SSc-ILD**. SSc is a rare, heterogeneous, multisystem, autoimmune, fibrotic connective tissue disease with a prevalence of 50 to 300 cases per million in the US and incidence of 2.3 to 22.8 cases per 1 million persons per year.[39] Up to 90% of patients with SSc develop ILD, predominantly women aged 30 to 55 years. In one cohort study, 9% of patients developed SSc at ≥65 years of age.[40] The median survival of patients with SSc-ILD is 5–8 years.[7] The most common histopathologic subtype of SSc-ILD is nonspecific interstitial pneumonitis. A less common subtype is usual interstitial pneumonitis, which is associated with worse survival.[19]
- **Place in Therapy Based on Medical Society Guidelines**. No medical society guidelines on the management of SSc-ILD included tocilizumab.

- **Potential Place in Therapy Based on the Evidence**. There have been no active-controlled trials to inform the place in therapy of tocilizumab in the treatment of SSc. In adults who had early, active / progressive, diffuse cutaneous SSc with increased inflammatory markers and who were mainly naïve to mycophenolate mofetil and cyclophosphamide, tocilizumab was numerically but not statistically effective for skin fibrosis and seemed to produce a sustained, clinically meaningful but statistically inconclusive benefit over placebo in preserving pulmonary function both in the overall population (SSc with or without ILD) and the post hoc subgroup of patients with ILD. The response in the ILD subgroup drove the favorable results observed in the overall population; however, the quality of evidence in the ILD subgroup was low. Tocilizumab seemed to improve HRCT-quantitated lung fibrosis, the time to treatment failure, and overall health status (ACR-CRISS), and to reduce the use of immunomodulator rescue therapy. There is insufficient data on the safety and efficacy of combination therapy, such as tocilizumab and another immunosuppressant effective for skin fibrosis (e.g., mycophenolate or cyclophosphamide). There is no evidence to inform the optimal timing for initiating therapy and the safety and efficacy of tocilizumab in patients with later stages of disease, patients previously exposed to mycophenolate or cyclophosphamide, or patients without increased acute phase reactants.
- **Potential Place in Therapy in VHA**. Tocilizumab therapy may be considered to preserve pulmonary function in patients with clinically evident SSc-ILD or subclinical SSc-ILD.

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