SUPPLEMENTARY APPENDIX

Table S1. Baseline characteristics of patients in each case series

	France		Brazil		Italy		Mexico		United Kingdom		United States of America	
	RA-ILD	RA-noILD	RA-ILD	RA-noILD	RA-ILD	RA-noILD	RA-ILD	RA-noILD	RA-ILD	RA-noILD	RA-ILD	RA-noILD
No. patients	100	165	61	201	46	47	33	69	18	29	152	162
Female — no. (%)	56 (56.0)	131 (79.4)	43 (70.5)	201 (100.0)	27 (58.7)	35 (74.5)	24 (72.7)	64 (92.8)	10 (55.6)	19 (65.5)	82 (53.9)	102 (63.0)
Age at inclusion — yr	60 (53-68)	55 (46-65)	58 (52-66)	62 (55-68)	71 (63-74)	72 (62-77)	56 (48-65)	55 (44-62)	74 (70-78)	69 (64-74)	68 (60-74)	69 (61-76)
RA duration — yr	10 (4-18)	10 (4-16)	14 (9-25)	17 (11-27)	16 (12-22)	17 (12-22)	10 (7-17)	12 (7-17)	8 (4-12)	10 (6-20)	12 (5-20)	10 (5-19)
MTX exposure duration — yr	4 (1-13)	10 (4-16)	8 (3-17)	17 (11-27)	9 (5-17)	17 (12-22)	7 (3-12)	12 (7-17)	5 (2-10)	10 (6-20)	6 (1-15)	10 (5-19)
Age at RA onset — yr	54 (44-62)	42 (30-52)	50 (41-57)	42 (32-50)	54 (46-66)	53 (46-61)	49 (29-57)	40 (31-47)	70 (57-75)	57 (49-62)	59 (49-69)	56 (44-63)
No. missing	0	1	0	0	0	0	0	0	0	0	0	0
Periods of MTX use at year of RA onset — no. (%)												
Unlikely	6 (6.0)	19 (11.5)	5 (8.2)	23 (11.4)	8 (17.4)	2 (4.3)	3 (9.1)	3 (4.3)	0 (0)	0 (0)	9 (5.9)	11 (6.8)
Less often	18 (18.0)	24 (14.5)	14 (23.0)	42 (20.9)	5 (10.9)	8 (17.0)	3 (9.1)	6 (8.7)	2 (11.1)	4 (13.8)	27 (17.8)	19 (11.7)
Often	42 (42.0)	81 (49.1)	23 (37.7)	88 (43.8)	26 (56.5)	28 (59.6)	12 (36.4)	35 (50.7)	4 (22.2)	10 (34.5)	61 (40.1)	52 (32.1)
Standard of care	34 (34.0)	41 (24.8)	19 (31.1)	48 (23.9)	7 (15.2)	9 (19.1)	15 (45.5)	25 (36.2)	12 (66.7)	15 (51.7)	55 (36.2)	80 (49.4)
Ever smoker — no. (%)	59 (59.0)	70 (45.2)	30 (50.0)	61 (31.3)	22 (51.2)	20 (43.5)	14 (42.4)	19 (27.5)	14 (77.8)	14 (53.8)	96 (64.0)	94 (58.0)
No. missing	0	10	1	6	3	1	0	0	0	3	2	0
Mean tobacco exposure (SD), pack/yr	13.8 (17.0)	10.0 (21.2)	18.9 (28.6)	7.6 (18.8)	0.5 (2.6)	0.0 (0.0)	5.4 (10.7)	1.3 (3.9)	21.9 (17.9)	14.1 (19.8)	19.6 (22.9)	14.4 (20.4)
	2	33	9	33	24	21	1	2	4	6	22	28
Biologic ever use	37 (57.8)	86 (55.5)	19 (31.1)	116 (57.7)	20 (48.8)	28 (66.7)	3 (9.1)	1 (1.4)	10 (55.6)	15 (51.7)	97 (63.8)	96 (59.3)
No. missing	36	10	0	0	5	5	0	0	0	0	0	0
Methotrexate exposure												
MTX ever use — no. (%)	60 (60.0)	137 (83.0)	44 (72.1)	194 (96.5)	40 (87.0)	47 (100.0)	32 (97.0)	68 (98.6)	18 (100.0)	29 (100.0)	113 (74.3)	147 (90.7)
MTX cumulative dose — g	0.1 (0.0-3.1)	2.2 (0.2-5.5)	2.1 (0.0-5.2)	4.8 (1.4-9.6)	0.7 (0.0-1.3)	2.9 (0.6-6.3)	1.9 (1.0-3.4)	5.2 (3.3-7.2)	4.5 (2.0-7.3)	5.2 (3.8-6.8)	2.1 (0.0-6.7)	3.9 (0.7-8.3)
No. missing	19	43	20	64	5	0	0	0	0	0	42	28
RA autoimmunity												
ACPA-positive — no. (%)	83 (85.6)	140 (88.1)	38 (76.0)	140 (75.3)	34 (73.9)	36 (76.6)	15 (75.0)	44 (100.0)	10 (71.4)	16 (66.7)	107 (85.6)	110 (78.0)
No. missing	3	6	11	15	0	0	13	25	4	5	27	21
RF-positive — no. (%)	71 (77.2)	120 (77.4)	43 (86.0)	113 (74.3)	38 (82.6)	39 (83.0)	22 (95.7)	56 (90.3)	18 (100.0)	24 (85.7)	108 (82.4)	114 (74.0)
No. missing	8	10	11	49	0	0	10	7	0	1	21	8
UIP or possible UIP — no. (%)	47 (52.8)		28 (45.9)		18 (39.1)		12 (36.4)		10 (55.6)		65 (42.8)	
No. missing	11		0		0		0		0		0	
Pulmonary function testing												
FVC — % predicted	88 (66-102)		NA		84 (74-91)		60 (50-85)		93 (84-113)		74 (61-87)	
No. missing	35		NA		22		1		2		12	
DLCO — % predicted	59 (50-70)		NA		65 (54-68)		38 (21-72)		56 (46-68)		53 (40-68)	
No. missing	40		NA		19		19		2		19	
TLC — % predicted	81 (69-94)		NA		77 (65-89)		73 (62-83)		83 (76-87)		76 (67-86)	
No. missing	52		NA		39		28		2		46	

RA: rheumatoid arthritis, ILD: interstitial lung disease, RA-ILD: patients with rheumatoid arthritis associated interstitial lung disease, RA-noILD: rheumatoid arthritis patients without interstitial lung disease, MTX: methotrexate, ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, HRCT: high-resolution computed tomography, UIP: usual interstitial pneumonia, FVC: forced vital capacity, DL_{CO}: diffusion capacity of carbon monoxide, TLC: total lung capacity, NA: not assessed. Values are median (interquartile range) or else if indicated.

Table S2. Sensitivity analyses of the association between methotrexate ever use and interstitial lung disease in patients with rheumatoid arthritis.

	Discovery	Pooled replication	Combined
Sensitivity analysis	OR_{adj} (95% CI)	OR_{adj} (95% CI)	OR_{adj} (95% CI)
One-stage analysis with random case series effects	0.46 (0.24 to 0.90)	0.43 (0.21 to 0.84)	0.44 (0.28 to 0.70)
Removing replication samples with too few unexposed	0.46 (0.24 to 0.90)	0.39 (0.19 to 0.81)	0.43 (0.26 to 0.70)
Complete cases analysis	0.41 (0.19 to 0.88)	0.41 (0.20 to 0.81)	0.41 (0.24 to 0.68)

Odds ratios (OR_{adj}) are adjusted for age at RA onset, sex, ever smoking, biologic ever use, MTX exposure duration and periods of MTX use at year of RA onset.

To add further sensitivity analyses, we considered that all missing biologic use data would be either « no » or « yes » in the discovery sample, which are rather extreme assumptions. This corresponded to proportions of biologic use of 37% or 73% for RA-ILD, respectively, and 52.1% or 58.2% for RA-noILD, respectively. In the first case, the odds ratio in the discovery sample was increased to 0.52 (95%CI 0.27 to 1.00), and in the second case it was 0.43 (0.22 to 0.84). The combined odds ratios were 0.45 (0.28 to 0.74) and 0.41 (0.25 to 0.67), respectively.

Table S3. Effect of methotrexate ever use on the delay of onset of interstitial lung disease among patients with rheumatoid arthritis.

	MTX never use	MTX ever use	Adjusted Mean	
Sample	Mean (SD)	Mean (SD)	Difference (95% CI)	P_{adj}
Discovery	3.7 (7.1)	10.7 (9.3)	3.5 (1.4–5.6)	0.001
Pooled replication	4.2 (7.6)	11.5 (10.7)	3.5 (2.2–4.8)*	<0.001
Combined	4.0 (7.4)	11.4 (10.4)	3.6 (2.6–4.7)*	<0.001

MTX: methotrexate. Mean differences and P-values are adjusted for age at RA onset, sex, ever smoking, biologic ever use, MTX exposure duration and periods of MTX use at year of RA onset, and obtained by a single-stage model with a random effect for case series origin (*), pooled over multiply imputed datasets. * UK excluded from the Pooled validation and Combined analyses.

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