

## Treatment with tumour necrosis factor inhibitors is associated with a time-shifted retardation of radiographic spinal progression in patients with axial spondyloarthritis

Murat Torgutalp, Valeria Rios Rodriguez, Ani Dilbaryan, Fabian Proft, Mikhail Protopopov, Maryna Verba, Judith Rademacher, Hiltrun Haibel, Joachim Sieper, Martin Rudwaleit, Denis Poddubnyy

**Supplementary Table S1. The reliability of mSASSS status score as reflected by intraclass correlation coefficients.**

	Year 0		Year 2		Year 4		Year 6		Year 8		Year 10	
	R2	R3	R2	R3	R2	R3	R2	R3	R2	R3	R2	R3
<b>R1</b>	0.97 (0.96-0.97)	0.95 (0.93-0.96)	0.97 (0.96-0.98)	0.95 (0.94-0.96)	0.97 (0.96-0.98)	0.92 (0.88-0.94)	0.95 (0.93-0.97)	0.92 (0.89-0.94)	0.92 (0.87-0.95)	0.92 (0.87-0.95)	0.93 (0.89-0.95)	0.91 (0.87-0.94)
<b>R2</b>	-	0.93 (0.9-0.94)	-	0.93 (0.91-0.95)	-	0.90 (0.86-0.93)	-	0.88 (0.83-0.92)	-	0.84 (0.74-0.9)	-	0.90 (0.84-0.93)

**Supplementary Table S2. The reliability of mSASSS change score as reflected by the intraclass correlation coefficients.**

	Year 0-Year 2		Year 2-Year 4		Year 4-Year 6		Year 6-Year 8		Year 8-Year 10	
	R2	R3	R2	R3	R2	R3	R2	R3	R2	R3
<b>R1</b>	0.84 (0.79-0.88)	0.72 (0.63-0.79)	0.61 (0.42-0.73)	0.31 (-0.01-0.53)	0.60 (0.36-0.75)	0.50 (0.19-0.68)	0.61 (0.26-0.8)	0.84 (0.69-0.91)	0.52 (0.04-0.76)	0.54 (0.08-0.77)
<b>R2</b>	-	0.83 (0.77-0.87)	-	0.61 (0.42-0.73)	-	0.66 (0.45-0.79)	-	0.55 (0.14-0.76)	-	0.34 (-0.33-0.67)

**Supplementary Table S3. Progression in mSASSS in the whole axSpA group and in the subgroups according to ASDAS-CRP categories based on different definitions of TNFi exposure.**

	TNFi exposure definition*									
	Any TNFi use in the current 2-year interval		TNFi for $\geq 12$ months in the current 2-year interval		Any TNFi use in the previous 2-year interval		TNFi for $\geq 12$ months in the previous 2-year interval		TNFi for $\geq 12$ months in the previous and $\geq 12$ months in the current 2-year interval	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
<b>All patients</b>	0.73 $\pm$ 1.47 (n=394)	0.88 $\pm$ 1.71 (n=99)	0.77 $\pm$ 1.53 (n=417)	0.70 $\pm$ 1.47 (n=76)	0.82 $\pm$ 1.58 (n=398)	0.55 $\pm$ 1.29 (n=70)	0.83 $\pm$ 1.61 (n=421)	0.37 $\pm$ 0.61 (n=47)	0.79 $\pm$ 1.57 (n=463)	0.35 $\pm$ 0.63 (n=39)
<b>ASDAS Category**</b>										
<b>Inactive Disease</b>	0.72 $\pm$ 1.50 (n=48)	1.06 $\pm$ 1.70 (n=28)	0.87 $\pm$ 1.60 (n=52)	0.81 $\pm$ 1.55 (n=24)	1.03 $\pm$ 1.67 (n=49)	0.65 $\pm$ 1.51 (n=21)	1.07 $\pm$ 1.76 (n=56)	0.29 $\pm$ 0.57 (n=14)	0.92 $\pm$ 1.66 (n=66)	0.28 $\pm$ 0.59 (n=13)
<b>Low Disease Activity</b>	0.62 $\pm$ 1.44 (n=130)	0.56 $\pm$ 1.19 (n=37)	0.60 $\pm$ 1.40 (n=137)	0.64 $\pm$ 1.30 (n=30)	0.65 $\pm$ 1.48 (n=132)	0.36 $\pm$ 0.65 (n=26)	0.63 $\pm$ 1.45 (n=138)	0.42 $\pm$ 0.65 (n=20)	0.62 $\pm$ 1.41 (n=157)	0.38 $\pm$ 0.66 (n=14)
<b>High Disease Activity</b>	0.63 $\pm$ 1.06 (n=184)	0.83 $\pm$ 1.78 (n=24)	0.64 $\pm$ 1.09 (n=191)	0.80 $\pm$ 1.87 (n=17)	0.66 $\pm$ 1.10 (n=183)	0.80 $\pm$ 1.86 (n=17)	0.69 $\pm$ 1.20 (n=190)	0.43 $\pm$ 0.72 (n=10)	0.66 $\pm$ 1.18 (n=200)	0.44 $\pm$ 0.76 (n=9)
<b>Very High Disease Activity</b>	1.71 $\pm$ 2.76 (n=32)	1.63 $\pm$ 2.84 (n=10)	1.90 $\pm$ 2.87 (n=37)	0.20 $\pm$ 0.18 (n=5)	2.03 $\pm$ 2.96 (n=34)	0.28 $\pm$ 0.25 (n=6)	1.90 $\pm$ 2.87 (n=37)	0.22 $\pm$ 0.19 (n=3)	1.87 $\pm$ 2.81 (n=40)	0.22 $\pm$ 0.19 (n=3)

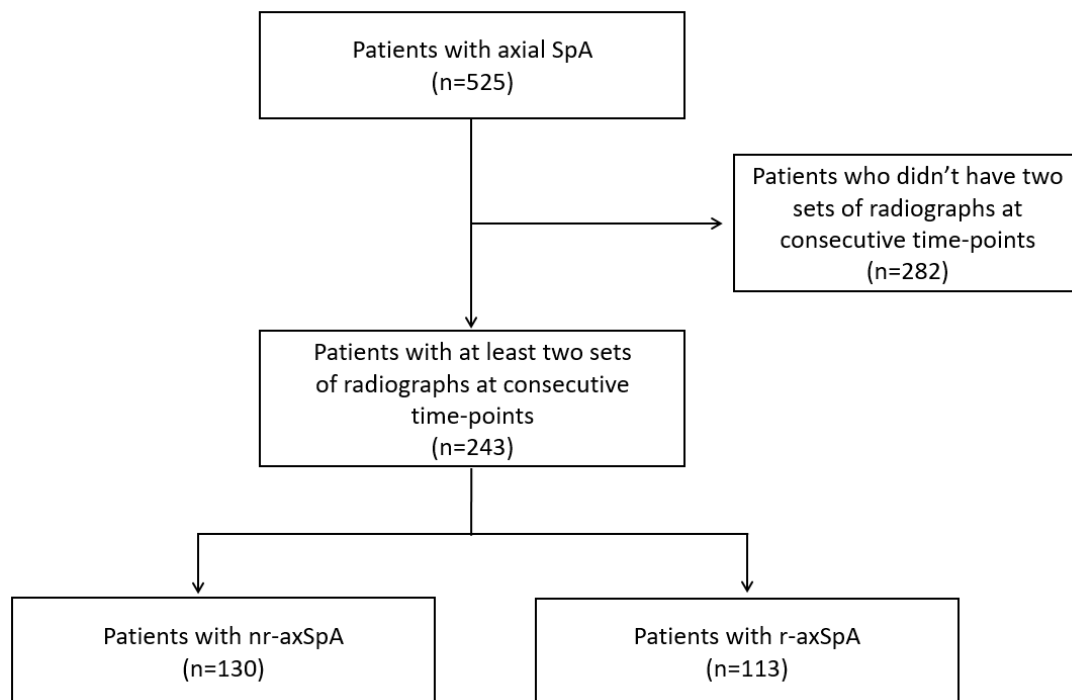
\* For all definitions of progression, available data regarding ASDAS in the current interval and data on TNFi exposure in the corresponding interval were used. The numerical differences regarding TNFi exposure between the current and the previous interval were due to missing information on TNFi in the previous interval.

\*\* Based on the time-averaged ASDAS in the current 2-year interval

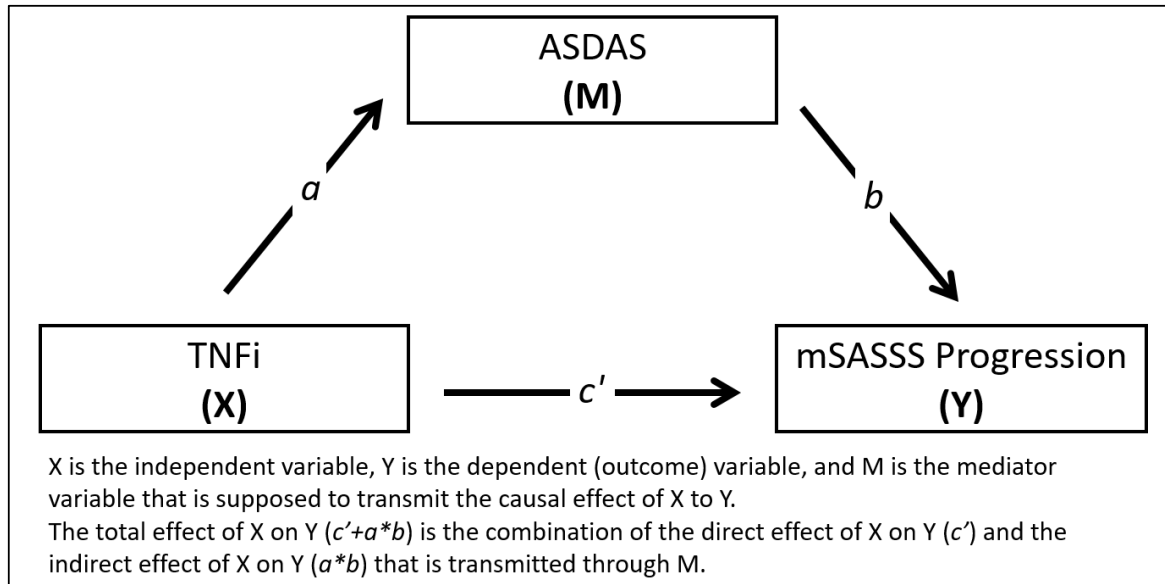
ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-Reactive Protein; mSASSS, Modified stoke ankylosing spondylitis spinal score; TNFi, tumour necrosis factor alpha inhibitor.

**Supplementary figure S1. Flowchart of the selection of included patients in the present analysis from the German SPondyloarthritis Inception Cohort (GESPIC).**

axSpA, axial Spondyloarthritis.



**Supplementary figure S2. A diagram to conceptualize the effect of TNFi exposure on spinal radiographic progression in the causal mediation analysis.**



ASDAS, Ankylosing Spondylitis Disease Activity Score; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; TNFi, tumour necrosis factor alpha inhibitor.

**Supplementary figure S3. The distribution of the intervals with respect to the definitions of the TNFi exposure of included 243 patients who contributed a total of 531 two-year radiographic intervals.**

TNFi, tumour necrosis factor alpha inhibitor.

Timepoints years	Y0	Y2	Y4	Y6	Y8	Y10	
	1. Interval (n=218)	2. Interval (n=126)	3. Interval (n=88)	4. Interval (n=55)	5. Interval (n=44)		TOTAL (n=531)
Any TNFi use in current 2-year interval (Yes/No)	30 / 188	20 / 106	16 / 72	19 / 36	18 / 26		103 / 428
TNFi ≥ 12 months in current 2-year interval (Yes/No)	11 / 207	17 / 109	13 / 75	19 / 36	18 / 26		78 / 453
Any TNFi use in previous 2-year interval (Yes/No)	8 / 210	20 / 86 20*	16 / 67 5*	13 / 40 2*	16 / 26 2*		73 / 429 29*
TNFi ≥ 12 months in previous 2-year interval (Yes/No)	0 / 218	10 / 96 20*	14 / 69 5*	9 / 44 2*	16 / 26 2*		49 / 453 29*
TNFi ≥ 12 months in previous and ≥ 12 months in current 2-year interval (Yes/No)	0 / 218	9 / 117	11 / 77	8 / 47	17 / 27		45 / 486

\* refers to the missing information regarding TNFi exposure in the previous interval.