

Supplementary appendix: Monocyte/macrophage subsets in the peripheral blood, their related cytokines, and circulating markers of fibrosis in active Takayasu Arteritis and longitudinal changes following immunosuppressive therapy

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Supplementary Table S1. Antibodies used for flow cytometry to identify monocytes/macrophages and monocyte/macrophage sub-populations.

Cell population	Primary Antibody	Conjugated Fluorochromes	Volume of Antibody Used (in μ L)
Neutrophils & eosinophils	anti-Human CD66b	PerCP-Cy5.5 G10F5	2.5
Overall population of monocytes/macrophages	anti-Human CD14	APC-H7 MphiP9	2.5
M1-like monocytes/macrophages	anti-Human CD80	PE-Cy7 L307.4	2.5
	anti-Human CD86	APC 2331(FUN-1)	8.5
	anti-Human TLR4 (CD284)	BV421 TF901	2.5
M2-like monocytes/macrophages	anti-Human MSR1 (CD204)	BV480	2.5
	anti-Human CD163	FITC GHI/61	2.5
	anti-Human CD206 (MMR)	PE	2.5

Supplementary Table S2. Comparison of overall monocytes/macrophage and monocyte/macrophage sub-populations between patients with TAK with active disease and healthy controls, and patients with TAK before (active TAK) and after immunosuppressive therapy (inactive TAK) - uncorrected and corrected p-values.

Population (%) Median with interquartile range (Q1-Q3)	Active TAK (n=18) vs HC (n=8)*		Active TAK vs Inactive TAK(n=18)**	
	p value	p value	p value	p value
	uncorrected	corrected	uncorrected	corrected
Monocytes/macrophages (CD14+ CD66b-) (% of leukocytes)	0.0000012802	0.0000064010	0.0000076294	0.0000381464
M1-like (CD80+ CD86+) (% of CD14+ CD66b- cells)	0.0000013800	0.0000069000	0.0000066291	0.0000331451
M1-like (CD80+ CD86+ TLR4+) (% of CD14+CD66b- cells)	0.0000011502	0.0000057510	0.0000592939	0.0002964343
M2-like (CD163+ CD206+) (% of CD14+ CD66b- cells)	0.0000010902	0.0000054510	0.0000041291	0.0000206453
M2-like (CD163+ CD206+ CD204+) (% of CD14+ CD66b- cells)	0.0000013902	0.0000069510	0.0000080230	0.0000401144
HC – Healthy controls, TAK – Takayasu arteritis				
*Mann-Whitney U test, **Wilcoxon matched-pairs signed rank test				

Supplementary Table S3. Comparison of overall monocytes/macrophage and monocyte/macrophage sub-populations between patients with TAK with active disease and healthy controls – subgroup including patients who were then treated with glucocorticoids and mycophenolate.

Population (%)	Healthy controls	Active TAK (n=16)	p value*
Median with interquartile range (Q1-Q3)	(n=8)		
Monocytes/macrophages (CD14+ CD66b-) (% of leukocytes)	3.32(3.01-4.81)	17.09(16.18-19.34)	< 0.001
M1-like (CD80+ CD86+) (% of CD14+ CD66b- cells)	1.21(1.09-1.85)	92.19(86.63-94.58)	< 0.001
M1-like (CD80+ CD86+ TLR4+) (% of CD14+CD66b- cells)	0.83(0.73-0.94)	88.65(85.88-90.97)	< 0.001
M2-like (CD163+ CD206+) (% of CD14+ CD66b- cells)	1.48(1.40-1.55)	6.97(6.81-7.17)	< 0.001
M2-like (CD163+ CD206+ CD204+) (% of CD14+ CD66b- cells)	0.036(0.029-0.40)	1.86(1.77-1.91)	< 0.001

TAK – Takayasu arteritis

Significant p values are highlighted in bold.

Values are presented as medians with interquartile range (Q1-Q3)

*Comparisons were performed using Mann–Whitney U Test; p<0.05, p values corrected for multiple testing

Supplementary Table S4. Comparison of overall monocytes/macrophage and monocyte/macrophage sub-populations between patients with TAK with active disease and healthy controls, and patients with TAK before (active TAK) and after immunosuppressive therapy (inactive TAK) - uncorrected and corrected p-values - subgroup including patients who were then treated with glucocorticoids and mycophenolate.

Population (%)	Active TAK (n=16) vs HC (n=8)*		Active TAK vs Inactive TAK(n=16)*	
	p-value	p-value	p-value	p-value
	uncorrected	corrected	uncorrected	corrected
Monocytes/macrophages (CD14+ CD66b-) (% of leukocytes)	0.0000027193	0.0000135964	0.0000305176	0.0001525787
M1-like (CD80+ CD86+) (% of CD14+ CD66b- cells)	0.0000019102	0.0000095510	0.0000215170	0.0001075804
M1-like (CD80+ CD86+ TLR4+) (% of CD14+CD66b- cells)	0.0000000002	<0.0000000001	0.0000102171	0.0000510845
M2-like (CD163+ CD206+) (% of CD14+ CD66b- cells)	0.0000012802	0.0000064010	0.0000076294	0.0000381464
M2-like (CD163+ CD206+ CD204+) (% of CD14+ CD66b- cells)	0.0000013104	0.0000065520	0.0000066190	0.0000330946

HC – Healthy controls, TAK – Takayasu arteritis

*Mann-Whitney U test, **Wilcoxon matched-pairs signed rank test

Supplementary Table S5. Mean Fluorescence Intensity (MFI) of monocyte/macrophage marker CD14, M1-like and M2-like monocyte/macrophage markers on overall peripheral blood mononuclear cells – uncorrected and corrected p values.

Monocyte/macrophage markers	Active TAK (n=18) vs HC(n=8)*		Active TAK vs Inactive TAK (n=18)**	
	p value	p value	p value	p value
	uncorrected	corrected	uncorrected	corrected
CD14	0.0000012802	0.0000089614	0.0000076294	0.0000534046
TLR4	0.0000014613	0.0000102291	0.0000074132	0.0000518912
CD80	0.0000016201	0.0000113406	0.0000066132	0.0000462915
CD86	0.0000017256	0.0000120791	0.0000041164	0.0000288144
CD204	0.0000015712	0.0000109983	0.0000063600	0.0000445192
CD206	0.0000016308	0.0000114155	0.0000053173	0.0000372205
CD163	0.0000015204	0.0000106428	0.0000083562	0.0000584919
HC – Healthy controls, TAK – Takayasu arteritis				
*Mann-Whitney U test, **Wilcoxon matched-pairs signed rank test				

Supplementary Table S6. Mean Fluorescence Intensity (MFI) of monocyte/macrophage marker CD14, M1-like and M2-like monocyte/macrophage markers on overall peripheral blood mononuclear cells - subgroup including patients who were then treated with glucocorticoids and mycophenolate – uncorrected and corrected p values.

Monocyte/macrophage markers	Active TAK (n=16) vs HC(n=8)*		Active TAK vs Inactive TAK (n=16)**	
	p value	p value	p value	p value
	uncorrected	corrected	uncorrected	corrected
CD14	0.0000027193	0.0000190349	0.0000305176	0.0002136036
TLR4	0.0000022061	0.0000154426	0.0000401066	0.0002807124
CD80	0.0000026128	0.0000182895	0.0000513008	0.0003590503
CD86	0.0000025706	0.0000179941	0.0000420310	0.0002941799
CD204	0.0000022082	0.0000154573	0.0000332154	0.0002324846
CD206	0.0000020451	0.0000143156	0.0000440816	0.0003085304
CD163	0.0000027393	0.0000191749	0.0000346069	0.0002422232
HC – Healthy controls, TAK – Takayasu arteritis				
*Mann-Whitney U test, **Wilcoxon matched-pairs signed rank test				

Supplementary Table S7. Comparison of absolute counts of overall monocytes/macrophage and monocyte/macrophage sub-populations in patients with TAK before (active TAK) and after immunosuppressive therapy (inactive TAK) – uncorrected and corrected p values.

Absolute population counts (per microlitre) Median with interquartile range (Q1-Q3)	Active TAK vs Inactive TAK (n=18)	
	p value	p value
	uncorrected*	corrected*
Monocytes/macrophages (CD14+ CD66b-)	0.0000076294	0.0000381464
M1-like (CD80+ CD86+)	0.0000076294	0.0000381464
M1-like (CD80+ CD86+ TLR4+)	0.0000076294	0.0000381464
M2-like (CD163+ CD206+)	0.0000076294	0.0000381464
M2-like (CD163+ CD206+ CD204+)	0.0000076294	0.0000381464
TAK – Takayasu arteritis		
*Wilcoxon matched-pairs signed rank test		

Supplementary Table S8. Comparison of overall monocytes/macrophage and monocyte/macrophage sub-populations between patients with TAK before (active TAK) and after immunosuppressive therapy (inactive TAK) – subgroup including patients who were then treated with glucocorticoids and mycophenolate.

Population (%)	Active TAK (n=16)	Inactive TAK (n=16)	p value*
Median with interquartile range (Q1-Q3)			
Monocytes/macrophages (CD14+ CD66b-) (% of leukocytes)	17.09(16.18-19.34)	7.13(5.98-7.95)	< 0.001
M1-like (CD80+ CD86+) (% of CD14+ CD66b- cells)	92.19(86.63-94.58)	1(0.93-1.14)	< 0.001
M1-like (CD80+ CD86+ TLR4+) (% of CD14+CD66b- cells)	88.65(85.88-90.97)	0.0018(0.0013-0.0024)	<0.001
M2-like (CD163+ CD206+) (% of CD14+ CD66b- cells)	6.97(6.81-7.17)	93.58(89.72-94.36)	< 0.001
M2-like (CD163+ CD206+ CD204+) (% of CD14+ CD66b- cells)	1.86(1.77-1.91)	91.78(90.05-94.10)	< 0.001
Significant p values are highlighted in bold.			
Values are presented as medians with interquartile range (Q1-Q3)			
*Comparisons were performed using Wilcoxon matched-pairs signed rank test; p<0.05, p values corrected for multiple testing			

Supplementary Table S9. Comparison of absolute counts of overall monocytes/macrophage and monocyte/macrophage sub-populations between patients before (active TAK) and after immunosuppressive therapy (inactive TAK) – subgroup including patients who were then treated with glucocorticoids and mycophenolate.

Absolute population counts (per microlitre)	Active TAK (n=16)	Inactive TAK (n=16)	p value*
Median with interquartile range (Q1-Q3)			
Monocytes/macrophages (CD14+ CD66b-)	1469 (1013 – 1721)	579 (391 – 765)	< 0.001
M1-like (CD80+ CD86+)	1330 (939 – 1621)	5.4 (4.5 – 8.2)	< 0.001
M1-like (CD80+ CD86+ TLR4+)	1283 (893 – 1579)	<1 (<1 - <1)	< 0.001
M2-like (CD163+ CD206+)	104 (70.4 – 122)	545 (358 – 705)	< 0.001
M2-like (CD163+ CD206+ CD204+)	27.7 (17.3 – 31.6)	527 (367 – 707)	< 0.001

Significant p values are highlighted in bold.

Values are presented as medians with interquartile range (Q1-Q3)

*Comparisons were performed using Wilcoxon matched-pairs signed rank test; p<0.05, p values corrected for multiple testing

Supplementary Table S10. Comparison of absolute counts of overall monocytes/macrophage and monocyte/macrophage sub-populations in patients with TAK before (active TAK) and after immunosuppressive therapy (inactive TAK) – subgroup including patients who were then treated with glucocorticoids and mycophenolate - uncorrected and corrected p values.

Absolute population counts (per microlitre)	Active TAK vs Inactive TAK (n=16)	
	p value	
	uncorrected*	corrected*
Median with interquartile range (Q1-Q3)		
Monocytes/macrophages (CD14+ CD66b-)	0.0000305176	0.0001525787
M1-like (CD80+ CD86+)	0.0000305176	0.0001525787
M1-like (CD80+ CD86+ TLR4+)	0.0000305176	0.0001525787
M2-like (CD163+ CD206+)	0.0000305176	0.0001525787
M2-like (CD163+ CD206+ CD204+)	0.0000305176	0.0001525787
TAK – Takayasu arteritis		
*Wilcoxon matched-pairs signed rank test		

Supplementary Table S11. Serum levels of M1-like cytokines, TNF- α , IL-1 β , IL-6, IP-10, IL-12p40, IL-23 and M2-like cytokines, IL-1RA and IL-10, and CCL17 – uncorrected and corrected p values.

Cytokines	Active TAK (n=18) vs HC (n=8)*		Active TAK vs Inactive TAK(n=18)**	
	p value	p value	p value	p value
	uncorrected	corrected	uncorrected	corrected
TNF- α	0.0000243235	0.0002188902	0.0000152588	0.0001373208
IL-1 β	0.1317188075	0.7194931015	0.0009918213	0.0088910600
IL-6	0.0000243235	0.0002188902	0.0006713867	0.0060262783
IP-10	0.1285228273	0.7100626655	0.0047454834	0.0419075577
IL-12p40	0.0087551807	0.0760927510	0.0002517700	0.0022636494
IL-23	0.0002214719	0.0019914822	0.0000076294	0.0000686625
IL-1RA(CD121a)	0.0000243235	0.0002188902	0.0089645386	0.0778474896
IL-10	0.0126661439	0.1083872613	0.0000076294	0.0000686625
CCL-17	0.0007431470	0.0066684758	0.0000534058	0.0004805495

HC – Healthy controls, TAK – Takayasu arteritis

*Mann-Whitney U test, **Wilcoxon matched-pairs signed rank test

Supplementary Table S12. Serum levels of M1-like cytokines, TNF- α , IL-1 β , IL-6, IP-10, IL-12p40, IL-23 and M2-like cytokines, IL-1RA and IL-10, and CCL17 – uncorrected and corrected p values – subgroup including patients who were then treated with glucocorticoids and mycophenolate.

Cytokines	Active TAK (n=16) vs HC(n=8)*		Active TAK vs Inactive TAK (n=16)**	
	p value	p value	p value	p value
	uncorrected	corrected	uncorrected	corrected
TNF- α	0.0000516676	0.0004649123	0.0000610352	0.0005491827
IL-1 β	0.2195191925	0.8925367300	0.0039672852	0.0351441642
IL-6	0.0000516676	0.0004649123	0.0026855469	0.0239119047
IP-10	0.1719279210	0.8169316481	0.0130920410	0.1118427557
IL-12p40	0.0182400122	0.1526790318	0.0007629395	0.0068455380
IL-23	0.0004799645	0.0043113966	0.0000305176	0.0002746249
IL-1RA(CD121a)	0.0000516676	0.0004649123	0.0249633789	0.2034952908
IL-10	0.0219043307	0.1807206210	0.0000305176	0.0002746249
CCL-17	0.0008892261	0.0079746279	0.0002136230	0.0019209650
HC – Healthy controls, TAK – Takayasu arteritis				
*Mann-Whitney U test, **Wilcoxon matched-pairs signed rank test				

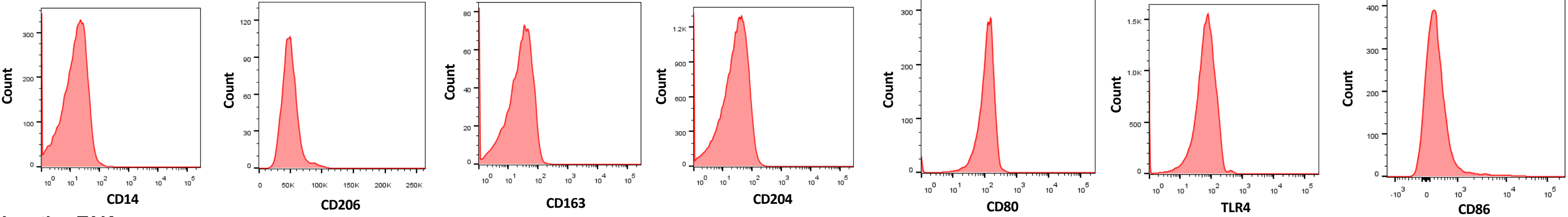
Supplementary Table S13. Plasma levels of circulating markers of fibrosis, individual components of the Enhanced Liver Fibrosis score (Hyaluronic Acid (HA), tissue inhibitor of metalloproteinases-1 (TIMP-1), procollagen type III N-terminal propeptide (PIIINP), and serum levels of TGF- β – corrected and uncorrected p values.

Circulating markers of fibrosis	Active TAK (n=18) vs HC(n=8)*		Active TAK vs Inactive TAK (n=18)**	
	p value		p value	
	uncorrected		uncorrected	
	corrected		corrected	
HA	0.0007796323	0.0031148841	0.0003280640	0.0013116104
TIMP-1	0.0152751596	0.0597148576	0.0000076294	0.0000305173
PIIINP	0.0016808820	0.0067065948	0.0000152588	0.0000610338
TGF- β	0.0132883135	0.0521031329	0.0000228882	0.0000915497
HC – Healthy controls, TAK – Takayasu arteritis				
*Mann-Whitney U test, **Wilcoxon matched-pairs signed rank test				

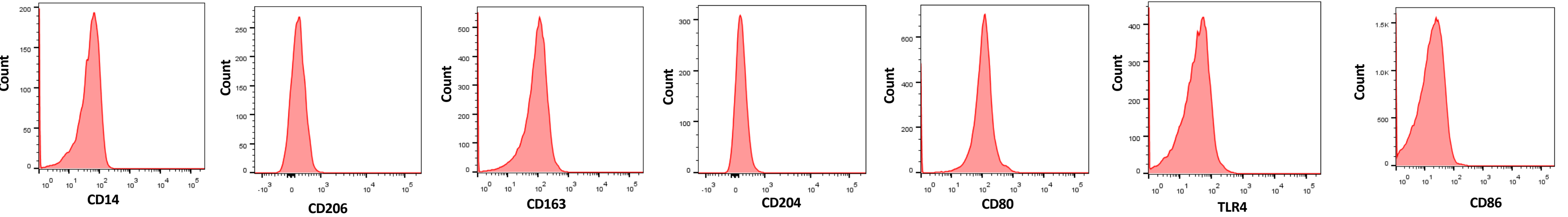
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Circulating markers of fibrosis	Active TAK (n=16) vs HC (n=8)*		Active TAK vs Inactive TAK (n=16)**	
	p value		p value	
	uncorrected		uncorrected	
	corrected		corrected	
HA	0.0009436130	0.0037691129	0.0013122559	0.0052387005
TIMP-1	0.0312955915	0.1194275278	0.0000305176	0.0001220648
PIIINP	0.0035623430	0.0141734109	0.0000610352	0.0002441184
TGF- β	0.0191768268	0.0745288770	0.0000915527	0.0003661605
HC – Healthy controls, TAK – Takayasu arteritis				
*Mann-Whitney U test, **Wilcoxon matched-pairs signed rank test				

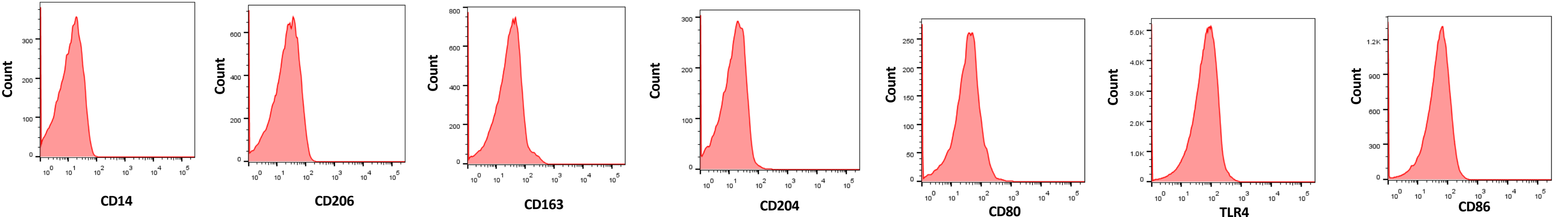
A. Active TAK



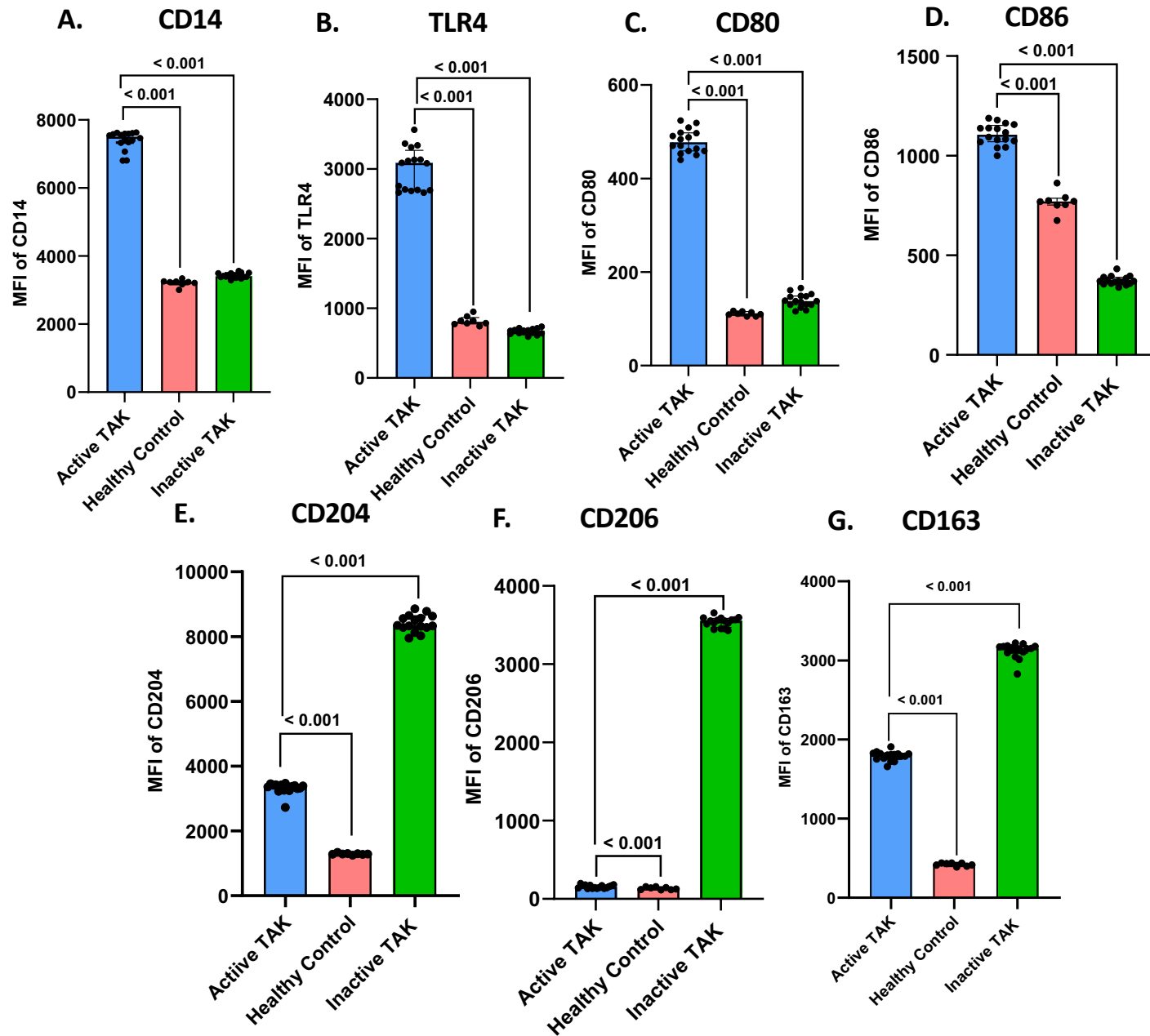
b. Inactive TAK



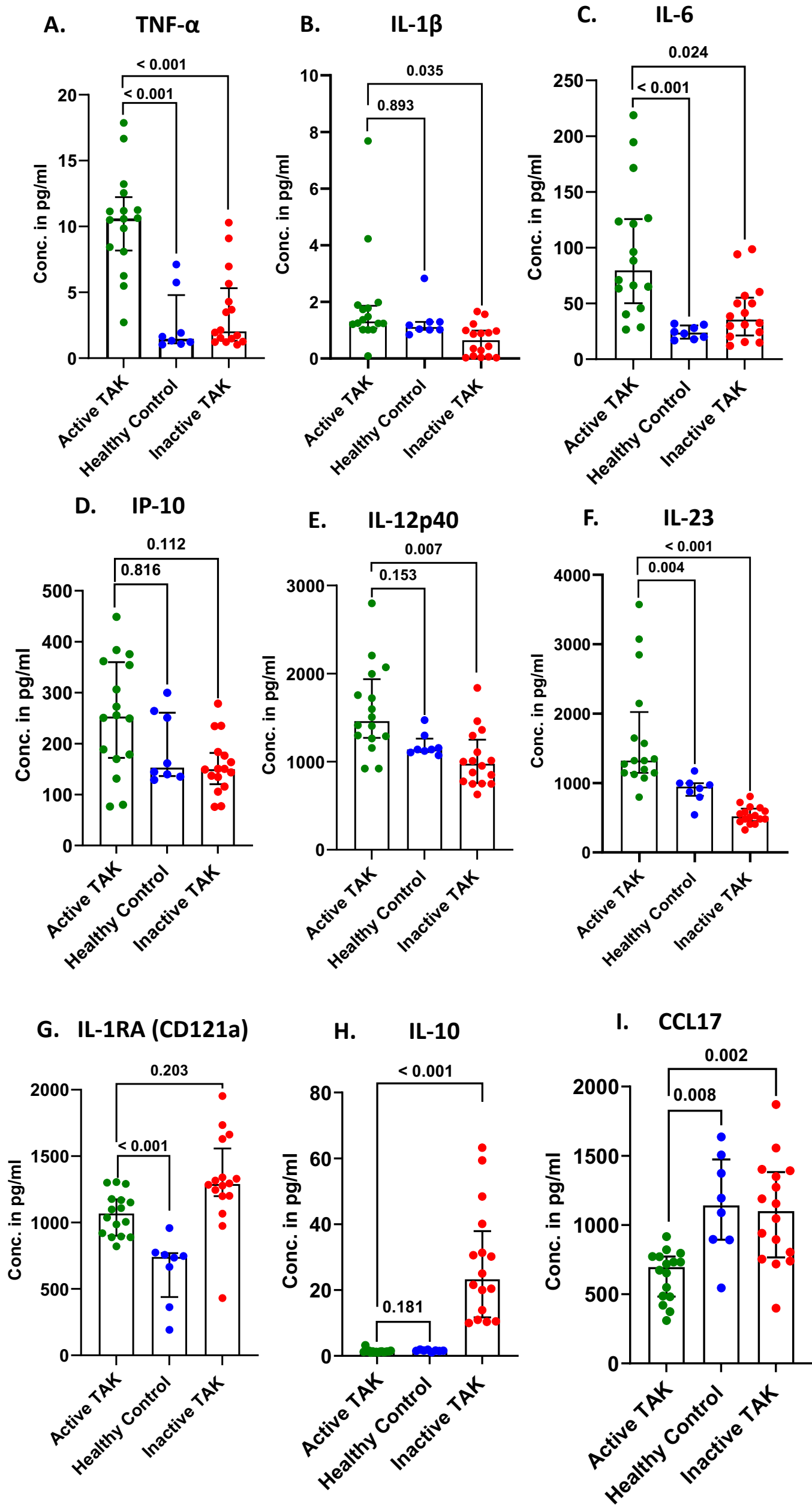
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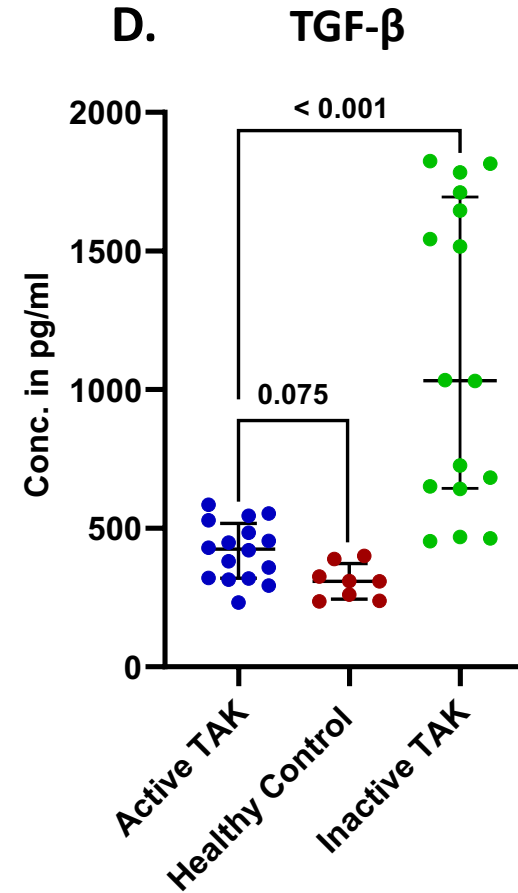
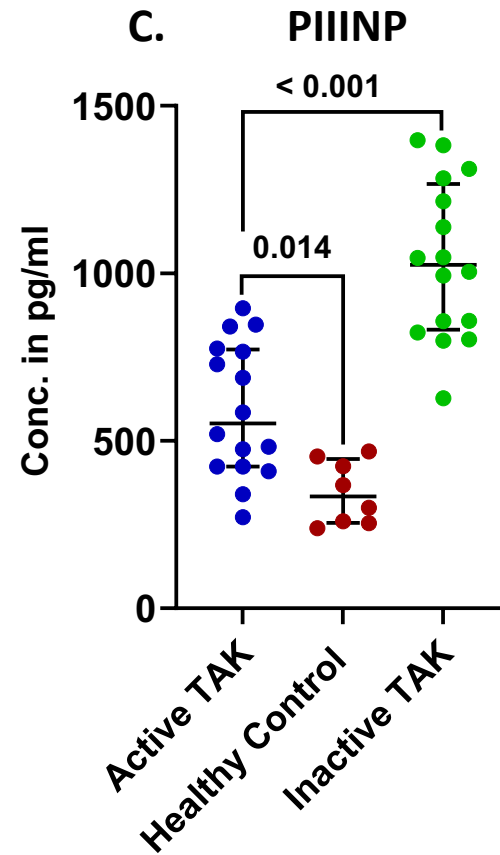
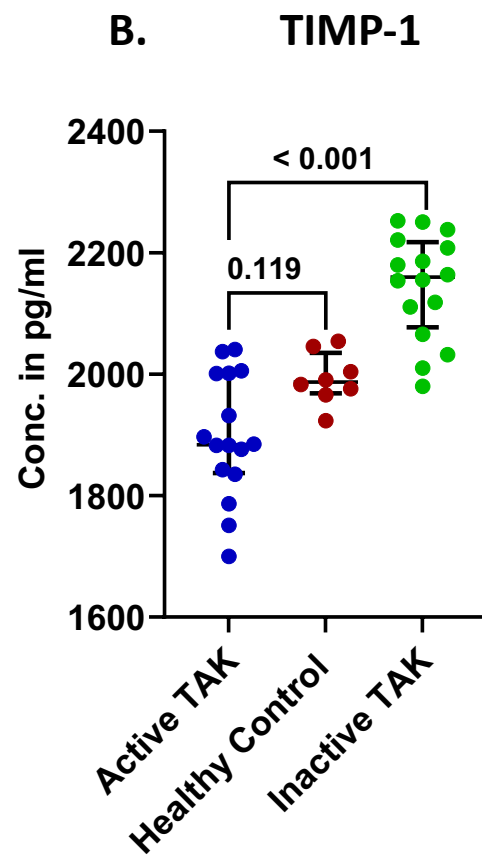
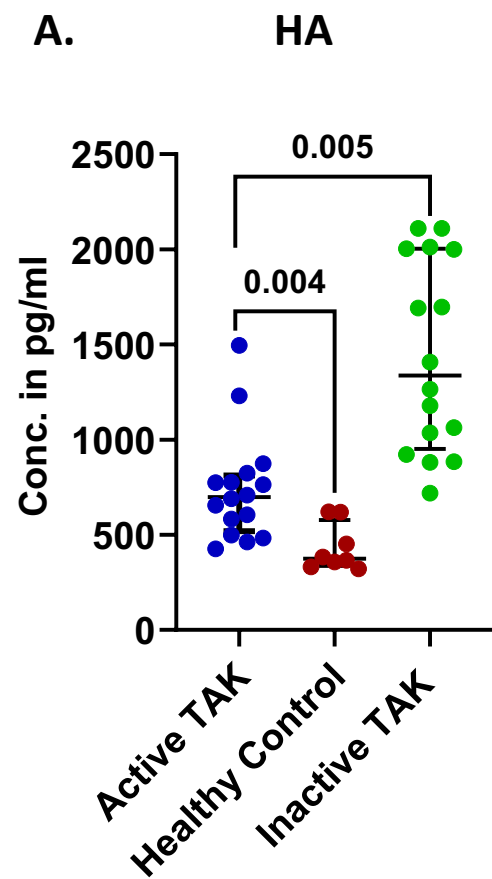
Supplementary Figure S1. Representative histograms showing the mean fluorescence intensity (MFI) for isotype controls for surface expression of CD14 monocyte/macrophage marker, M1-like (CD80, CD86 & TLR4) and M2-like (CD163, CD204 & CD206) monocyte/macrophage markers for patients with active TAK (A), inactive TAK (B) and healthy controls (C). The x-axis indicates fluorescence intensity for each marker, while the y-axis shows cell counts.



Supplementary Figure S2: Mean Fluorescence Intensity (MFI) of monocyte/macrophage marker CD14, M1-like and M2-like monocyte/macrophage markers on overall peripheral blood mononuclear cells - subgroup including patients treated with glucocorticoids and mycophenolate. (A) CD14 (B) TLR4 (C) CD80 (D) CD86 (E) CD204 (F) CD206 (G) CD163. Delta MFI (MFI of the marker minus that of the corresponding isotype control) are plotted. Comparison were made between patients with TAK & healthy controls using Mann–Whitney U Test and between patients with TAK before and after immunosuppressive therapy using Wilcoxon matched pairs signed rank test, p values were corrected for multiple testing using the Bonferroni-Sidak method.



Supplementary Figure S3. Serum levels of M1-like cytokines, TNF- α (A), IL-1 β (B), IL-6 (C), IP-10 (D), IL-12p40(E), IL-23(F) and M2-like cytokines, IL-1RA(G) and IL-10 (H), and CCL17(I) - subgroup including patients treated with glucocorticoids and mycophenolate. Comparison were made between patients with active TAK & healthy controls using Mann–Whitney U Test and between patients with TAK before (active disease) and after immunosuppressive therapy (inactive disease) using Wilcoxon matched pairs signed rank test, p values were corrected for multiple testing using the Bonferroni-Sidak method.



Supplementary Figure S4: Plasma levels of circulating markers of fibrosis, individual components of the Enhanced Liver Fibrosis score (Hyaluronic Acid (HA) (A), tissue inhibitor of metalloproteinases-1 (TIMP-1) (B), procollagen type III N-terminal propeptide (PIIINP) (C), and serum levels of TGF- β (D) - subgroup including patients treated with glucocorticoids and mycophenolate. Comparison were made between patients with active TAK & healthy controls using Mann–Whitney U Test and between patients with TAK before (active disease) and after immunosuppressive therapy (inactive disease) using Wilcoxon matched pairs signed rank test, p values were corrected for multiple testing using the Bonferroni-Sidak method.