E.1 Immunomodulatory drugs (rituximab, rintatolimod, IV immunoglobulin G) versus placebo

Figure 2: Quality of Life: SF36 (max % change from baseline) at 10 months (rituximab)

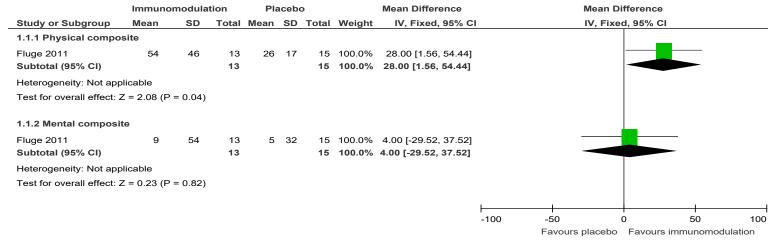


Figure 3: Fatigue/fatigability: Fatigue severity scale at 18 months (rituximab)

				Mean Difference		Mea	an Differen	се	
Study or Subgroup	Mean Difference	SE	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
Fluge 2019	-0.07	1.6021	100.0%	-0.07 [-3.21, 3.07]					
Total (95% CI)			100.0%	-0.07 [-3.21, 3.07]			•		
Heterogeneity: Not ap Test for overall effect:					-50 Favours ir	-25 nmunomodulat	0 ory Favo	25 urs placebo	50

Figure 4: Fatigue/fatigability: Fatigue numeric rating scale 0-10 at 16-20 months (rituximab)

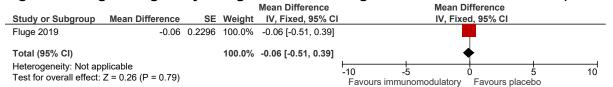


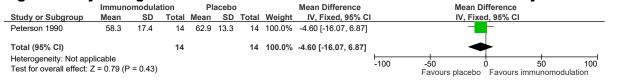
Figure 5: Psychological status: Hamilton Depression Scale at 6 months (IVIG)

0 .	Immuno	modula	tion	Pla	aceb	0		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	I IV, Fixed, 95% CI
Lloyd 1990	9	5	23	10	3	26	100.0%	-1.00 [-3.35, 1.35]	
Total (95% CI)			23			26	100.0%	-1.00 [-3.35, 1.35]	•
Heterogeneity: Not app Test for overall effect:		= 0.40)							-20 -10 0 10 20 Favours immunomodulation Favours placebo

Figure 6: Psychological status: Zung Self-Rating Depression Scale at 6 months (IVIG)

	Immuno	modula	tion	Pla	acebo	D		Mean Difference		N	lean Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		ľ	/, Fixed, 95%	CI	
Lloyd 1990	41	11	23	40	12	26	100.0%	1.00 [-5.44, 7.44]					
Total (95% CI)			23			26	100.0%	1.00 [-5.44, 7.44]			•		
Heterogeneity: Not app		- 0 70)							-50	-25	0	25	50
Test for overall effect: 2	2 = 0.30 (P	= 0.76)							Favours	; immunomodu	ation Favou	rs placebo	

Figure 7: Psychological status: mental health on the Medical Outcome Study Short Form at 150 days (IVIG)



0

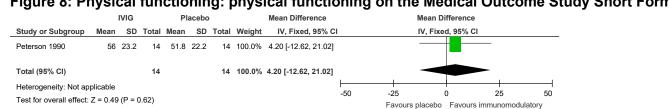


Figure 8: Physical functioning: physical functioning on the Medical Outcome Study Short Form at 150 days (IVIG)

Figure 9: Physical functioning: physical functioning on the SF36 at 24 months (rituximab)

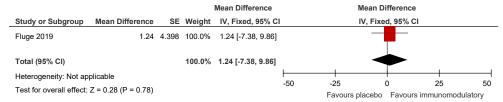


Figure 10: Physical functioning: functional level % at 16-20 months (rituximab)

				Mean Difference		Me	ean Difference)	
Study or Subgroup	Mean Difference	SE	Weight	IV, Fixed, 95% CI		IV	, Fixed, 95% C		
Fluge 2019	-0.68	2.6633	100.0%	-0.68 [-5.90, 4.54]					
Total (95% CI)			100.0%	-0.68 [-5.90, 4.54]			•		
Heterogeneity: Not app Test for overall effect: Z					-100	-50 Favours pla	0 cebo Favour	50 50 s immunomodi	100 ulatory

Figure 11: SAEs with possible/probable relation to intervention (rintatolimod)

	Immunomodu	lation	Place	bo		Risk Ratio		Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fiz	ked, 95% Cl		
Strayer 2012	1	117	2	117	100.0%	0.50 [0.05, 5.44]					
Total (95% CI)		117		117	100.0%	0.50 [0.05, 5.44]					
Total events	1		2								
Heterogeneity: Not ap	plicable						H	+	+	+	
Test for overall effect:	Z = 0.57 (P = 0.5	57)					0.01 Favours	0.1 immunomodulation	1 Favours pla	10 icebo	100

Figure 12: Adverse events: major adverse events (IVIG)

	Immunomodu	lation	Placel	bo		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95% Cl		
Peterson 1990	3	15	3	15	100.0%	1.00 [0.24, 4.18]					
Total (95% CI)		15		15	100.0%	1.00 [0.24, 4.18]					
Total events	3		3								
Heterogeneity: Not app	olicable								+	+	
Test for overall effect:	Z = 0.00 (P = 1.0	0)					0.01 Favours imn	0.1 nunomodulation	Favours pla	10 cebo	100

Figure 13: Adverse events: constitutional symptoms (IVIG)

-	Immunomodu	lation	Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Vollmer-Conna 1997	56	73	23	26	100.0%	0.87 [0.72, 1.05]	
Total (95% CI)		73		26	100.0%	0.87 [0.72, 1.05]	◆
Total events Heterogeneity: Not app Test for overall effect: 2		4)	23				0.2 0.5 1 2 5 Favours immunomodulation Favours placebo

Figure 14: Adverse events: any SAEs with possible/probable relation to intervention (rituximab)

U	Immunomodu	lotom/	Placel	ha		Peto Odds Ratio	Data O	dds Ratio	•
	Immunomodu	atory	Placel	00		Peto Odds Ratio	Pelo U		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fix	ced, 95% Cl	
Fluge 2019	8	77	0	74	100.0%	7.82 [1.89, 32.35]			-
Total (95% CI)		77		74	100.0%	7.82 [1.89, 32.35]			-
Total events	8		0						
Heterogeneity: Not app	licable						0.02 0.1	1 10	50
Test for overall effect: 2	Z = 2.84 (P = 0.0	05)					Favours immunomodulatory	Favours placebo	50

Figure 15: Adverse events: any AEs of at least moderate severity with possible/probable relation to intervention (rituximab)

	Immunomodula	atory	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Fluge 2019	26	77	12	74	100.0%	2.08 [1.14, 3.81]	
Total (95% CI)		77		74	100.0%	2.08 [1.14, 3.81]	
Total events	26		12				
Heterogeneity: Not app Test for overall effect:		!)					I I

Figure 16: Adverse events: suspected unexpected adverse reactions (rituximab)

-	Immunomodula	atory	Place	bo		Risk Ratio		Risk	Ratio		-	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% (
Fluge 2019	2	77	1	74	100.0%	1.92 [0.18, 20.75]						→
Total (95% CI)		77		74	100.0%	1.92 [0.18, 20.75]						
Total events	2		1									
Heterogeneity: Not ap Test for overall effect:)					 l 0.2 s immunomo	0.5 odulatory	1 Favours	2 placebo	5	10

Figure 17: Activity levels: mean steps/24 hrs (rituximab)

0	•			Mean Difference	,	Mean D	ifference		
Study or Subgroup	Mean Difference	SE	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% Cl		
Fluge 2019	-127	447.4572	100.0%	-127.00 [-1004.00, 750.00]	•				
Total (95% CI)			100.0%	-127.00 [-1004.00, 750.00]					
Heterogeneity: Not ap Test for overall effect:					-1000	-500 Favours placebo		1 500 Inomodula	1000 atory

Figure 18: Exercise performance measure: Treadmill exercise duration in seconds at 42 weeks (rintatolimod)

	Immun	omodula	tion	P	lacebo			Mean Difference		M	ean Differen	се	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV	, Fixed, 95%	CI	
Strayer 2012	672	314.1	100	616	286.7	108	100.0%	56.00 [-25.94, 137.94]					
Total (95% CI)			100			108	100.0%	56.00 [-25.94, 137.94]					
Heterogeneity: Not app Test for overall effect:		P = 0.18)							-200	-100 Favours pla	0 Icebo Favo	100 urs immunom	200 odulation

Figure 19: Return to school or work: Resumption of pre-morbid employment status (full-time) at 6 months (IVIG)

		Immunomodulation		Placebo			Peto Odds Ratio	Peto Odds Ratio
_	Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
	Lloyd 1990	6	23	0	26	100.0%	10.79 [1.98, 58.68]	
	Total (95% CI)		23		26	100.0%	10.79 [1.98, 58.68]	
	Total events	6		0				
	Heterogeneity: Not app	licable						+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
	Test for overall effect: Z = 2.75 (P = 0.006)							Favours placebo Favours immunomodulation

Figure 20: Symptom scales: Marked reduction in symptoms and improvement in functional capacity (IVIG)

	Immunomodulation		Placebo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% Cl	
Lloyd 1990	10	23	3	26	100.0%	3.77 [1.18, 12.04]				
Total (95% CI)		23		26	100.0%	3.77 [1.18, 12.04]				
Total events	10		3							
Heterogeneity: Not applicable Test for overall effect: Z = 2.24 (P = 0.03)							0.05	0.2		20
							0.05	Favours placebo	Favours immune	