

**Biologic TNF- $\alpha$  inhibitors for Steven-Johnsons syndrome, Toxic Epidermal Necrolysis, and TEN-SJS overlap: a study level and patient level meta-analysis**

**Running title: Biologic TNF- $\alpha$  inhibitors for SJS/TEN.**

**Jiali Cao<sup>1,\*</sup>, Xuan Zhang<sup>1</sup>, Xinzhu Xing<sup>1</sup>, Jie Fan<sup>2</sup>**

**Affiliations**

1. Department of Dermatology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China
2. Medical Department, Shunyi Maternal and Children's Hospital of Beijing Children's Hospital, Beijing 101300, China.

**\*Corresponding Author**

**Jiali Cao**

Department of Dermatology, Beijing Chaoyang Hospital, Capital Medical University,  
No. 8 Gongti South Road, Chaoyang District, Beijing 100020, China

E-mail: [jialicao2302@163.com](mailto:jialicao2302@163.com)

Supplementary Table 1: Overview on the results of the quality assessment of the included studies (N = 55).

Item	Answers and their frequencies/percentages	
	Yes	No
1. Is the hypothesis/aim/objective of the study clearly described?	14 (25.5%)	41 (74.5%)
2. Are the main outcomes to be measured clearly described in the introduction or methods section?	48 (87.3%)	7 (12.7%)
3. Are any outcome (relevant for the outcome of the present systematic review) described?	55 (100%)	0 (0%)
4. Was a main outcome identified?	14 (25.5%)	41 (74.5%)
5. Are the inclusion and exclusion criteria clearly stated in the introduction or methods section?	7 (12.7%)	48 (87.3%)
6. What proportion of subjects who were approached were ineligible to participate?	4 (7.3%)	51 (92.7%)
7. What proportion of subjects who were eligible refused to participate?	0 (0%)	55 (100%)
8. Patients completed the allocated treatment regimen	2 (3.6%)	53 (96.4%)
Description of following confounding factor distribution for each group of patients		
9. Age	54 (98.2%)	1 (1.8%)
10. Severity	52 (84.5%)	3 (5.5%)
11. BSA	44 (80%)	11 (20%)
12. Years	55 (100%)	0 (0%)
13. Reporting of 95% CI and/ or P value for mortality data*	4 (7.3%)	51 (92.7%)

No description of item carries score 0, Description of each point score=1 except for reporting of mortality data where description of “95% CI and P value both” carries score - 0.67 and “only P value reporting” carries score - 0.33. BSA: Body surface area, CI: Confidence interval.

Supplementary Table 2: Detailed information on individual patient.

Author	Culprit drugs	Diagnosis	Age	Sex	BSA (%)	SCORTE N	Intervention	Dose	Days after onset therapy given	Combined therapy	Timing with combined therapy	Time of re-epithelialization (days)	Hospitalization time (days)	Outcome	Sequelae
Infliximab															
Gaitanis	Sulfamethoxazole/trimethoprim	SJS-TEN overlap	72	M	20	4	Infliximab	5 mg/kg one-time infusion	6	Corticosteroids + IVIG + Supportive therapy	Combined		22	Survived	
Paquet	Ibuprofen	SJS-TEN overlap	65	M	15		Infliximab	5 mg/kg one-time infusion	4	NAC	Combined	2		Death (7 days after admission)	
Patmanidis	Trimethoprim-sulfamethoxazole	SJS-TEN overlap	74	F	25	3	Infliximab	5 mg/kg one-time infusion	1	Corticosteroids + Supportive therapy	Combined		19	Survived	
Al-Shouli	Aphrodisiac herbal drugs and sildenafil	TEN	67	M	40		Infliximab	3 mg/kg one-time infusion	12	Supportive therapy	Combined	7	10	Survived	
Burduk	Trimetoprim plus sulphamethoxazole	TEN	17	F	80		Infliximab	5 mg/kg one-time infusion						Survived	Nasolacrimal duct obstruction
Cardenas	Ibuprofen and acetaminophen	TEN	4	F	90		Infliximab	8 mg/kg one-time infusion	14	Cyclosporine and IVIG	After	60	60	Survived	
Chafanska	Mycoplasma pneumoniae	TEN	4	M	30		Infliximab	5 mg/kg one-time infusion	5	Supportive therapy	Combined	6	11	Survived	Postinflammatory hyperpigmentation and dry eyes
Fischer	Co-trimoxazole	TEN	56	F	35		Infliximab	5 mg/kg one-time infusion	4					Survived	
Frederiks	Pantoprazole	TEN	68	M	40	4	Infliximab	5 mg/kg one-time infusion	1	Corticosteroids	Combined		7	Death (7 days after admission)	Gastrointestinal bleeding, hypotension, hypoglycaemia.
	Cefprozil	TEN	85	M	40	3	Infliximab	5 mg/kg one-time infusion	6	Corticosteroids + IVIG + Supportive therapy	Combined			Death with noticeably improved skin condition.	
	Sulfamethoxazole/trimethoprim	TEN	61	M	30	4	Infliximab	5 mg/kg one-time infusion	6	Corticosteroids + IVIG + Supportive therapy	Combined		21	Survived	None

Hunger	Diclofenac for headache	TEN	69	F	30		Infliximab	5 mg/kg one-time infusion	4			5		Survived	
Jiang	Methazolamide-induced	TEN	36	M	35		Infliximab	4 mg/kg once and a second dose of at 5 mg/kg	3	Supportive therapy + Corticosteroids	After	7	21	Survived	
Kreft	Etoricoxib for pain of herniated disk	TEN	31	M	50		Infliximab	5 mg/kg one-time infusion		Corticosteroids	After	35		Survived	No lasting ophthalmological or urological sequels
Kreft		TEN	11	F			Infliximab	250 mg one-time infusion	3	Corticosteroids + IVIG	After	14		Survived	In addition to ophthalmic complications with entropion and increasing corneal neovascularization, hypertrophic, partially keloidal scarring on the skin was observed within 4 months
Kumar	Pembrolizumab	TEN	57	F	80		Infliximab	5 mg/kg one-time infusion		Corticosteroids	After	None		Decision was made to focus care on comfort only	
Paquet	Nadroparine	TEN	88	F	30		Infliximab	5 mg/kg one-time infusion	2	NAC	Combined	2		A	
	Tramadol	TEN	23	F	50		Infliximab	5 mg/kg one-time infusion	13	NAC	Combined	2		A	
	Fluconazole	TEN	50	F	60		Infliximab	5 mg/kg one-time infusion	7	NAC	Combined	2		A	
	Amoxicilline	TEN	60	M	50		Infliximab	5 mg/kg one-time infusion	7	NAC	Combined	2		Death (9 days after admission)	
Plant	Fluconazole or penicillin	TEN	32	F			Infliximab	5 mg/kg one-time infusion	8	IVIG + Supportive therapy	After			Survived despite poor prognostic indicators	Pneumonia, septicaemia and hepatitis. Liver biopsy confirmed vanishing bile duct

															syndrome, thought to be either secondary to a drug-induced hepatitis or as a direct consequence of TEN.
Scott-Lang	Carbamazepine for epilepsy	TEN	7	M			Infliximab	5 mg/kg one-time infusion	4	IVIG + Supportive therapy	Combined	10	15	Survived	None
Scott-Lang	Carbamazepine	TEN	7	M			Infliximab	5 mg/kg one-time infusion	4	IVIG + Supportive therapy	Combined	10	30	Survived	No long-term sequelae and, in particular, no scarring of skin or conjunctivae
Vivar	Nivolumab for treatment of metastatic melanoma; anti-pd1 therapy	TEN	50	F	90	5	Infliximab	5 mg/kg one-time infusion		IVIG + corticosteroids	Combined			Death	
Wallenborn	Allopurinol, ibuprofen, and etoricoxib	TEN	44	M	80	2	Infliximab	5 mg/kg one-time infusion	4	Corticosteroids	After	28	28	Survived	
Wojtkiewicz	Co-trimoxazole	TEN	17	F	80		Infliximab	5 mg/kg one-time infusion	6	Corticosteroids + Supportive therapy	Combined	12	18	Survived	Hyperpigmentation
Worsnop	Sulfasalazine	TEN	32	F	30	2	Infliximab	5 mg/kg one-time infusion	2	IVIG	After	9	26	Survived	The infliximab treatment subsequently triggered erosive lichen planus (lp) involving the mouth and vulva.
Zárate-Correa	Furosemide	TEN	76	M	100	2	Infliximab	3 mg/kg one-time infusion	4	Supportive therapy		9		Survived	Infections
Adalimumab															
Kherlopian	Chadox1 ncov-19 (AZD1222) vaccine	TEN	48		90	3	Adalimumab	80 mg day 0, 40 mg day 3 & day 7	0			34	35	Survived	
	Febuxostat, lornoxicam,	TEN	30		80	2	Adalimumab	80 mg day 0	0	Corticosteroids + IVIG	Combined	20	23	Survived	

	pregabalin, naproxen														
	Lamotrigine	TEN	16		35	1	Adalimumab	40 mg day 0	0			9	15	Survived	
	Cefazolin, flucloxacillin, pembrolizumab	TEN	61		60	4	Adalimumab	80 mg	6	Corticosteroids	Combined	6	18	Resolution of TEN, Deceased due to progression of Stage IV NSCLC	
Etanercept															
Ao	Carbamazepine	SJS	24	M		1	Etanercept	25 mg twice a week		Corticosteroids	Combined		6	Survived	None
	Carbamazepine	SJS	44	M		3	Etanercept	25 mg twice a week		Corticosteroids	Combined		10	Survived	None
	Allopurinol	SJS	24	M		5	Etanercept	25 mg twice a week		Corticosteroids	Combined		12	Survived	None
	Lamotrigine	SJS	67	M		2	Etanercept	25 mg twice a week		Corticosteroids	Combined		12	Survived	None
	Carbamazepine	SJS	53	F		5	Etanercept	25 mg twice a week		Corticosteroids	Combined		8	Survived	None
	Nsaids	SJS	72	M		4	Etanercept	25 mg twice a week		Corticosteroids	Combined		14	Survived	None
	Carbamazepine	SJS	37	M		2	Etanercept	25 mg twice a week		Corticosteroids	Combined		13	Survived	None
	Carbamazepine	SJS	57	F		4	Etanercept	25 mg twice a week		Corticosteroids	Combined		10	Survived	None
	Lamotrigine	SJS	19	F		0	Etanercept	25 mg twice a week		Corticosteroids	Combined		15	Survived	None
	Tcm	SJS	28	F		0	Etanercept	25 mg twice a week		Corticosteroids	Combined		10	Survived	None
Dreyer	Mycoplasma				Mucosa 1 only	0	Etanercept	50 mg/ml one-time infusion				7		Survived	
	Trimethoprim-sulfa methoxazole				8	2	Etanercept	50 mg/ml one-time infusion		IVIG	Combined			Survived	
	Vancomycin vs				5	1	Etanercept	50 mg/ml				3		Survived	

	cefepime							one-time infusion							
	Piperacillin-tazobactam				9	0	Etanercept	50 mg/ml one-time infusion		IVIG	Combined			Survived	
	Trimethoprim-sulfamethoxazole				Mucosa l only	1	Etanercept	50 mg/ml one-time infusion						Survived	
Torres - Navarro	Allopurinol	SJS	20	F	10	4	Etanercept	50 mg/ml one-time infusion	9				15	Survived	
Wang	Lamotrigine and sodium valproate	SJS	28	F	10	0	Etanercept	50 mg/ml one-time infusion	14	IVIG	Combined	7		Survived	None
Ao	Nsaids	SJS/TEN overlap	33	F		3	Etanercept	25 mg twice a week		Corticosteroids	Combined		17	Survived	None
Chong	Nsaids	SJS/TEN overlap	77	M	15	2	Etanercept	50 mg/ml one-time infusion	7	Antibiotic		2	5	Survived	None
Dreyer	Trimethoprim-sulfamethoxazole	SJS/TEN overlap			20	2	Etanercept	50 mg/ml one-time infusion				7		Survived	
	Trimethoprim-sulfamethoxazole	SJS/TEN overlap			18	4	Etanercept	50 mg/ml one-time infusion		IVIG	Combined	29		Survived	
Gavigan	Sulfamethoxazole-trimethoprim	SJS/TEN overlap	11	F	25		Etanercept	25 mg, 2 doses, every other day	2	Corticosteroids	Combined	12		Survived	None
López-Gómez	Ribociclib-related	SJS/TEN overlap	77	F	20		Etanercept	40 mg one-time infusion		Corticosteroids	Combined	6		Survived	
Torres - Navarro	Lamotrigine	SJS/TEN overlap	16	F	20	1	Etanercept	50 mg/ml one-time infusion	1				11	Survived	
Ao	Carbamazepine	TEN	71	F		3	Etanercept	25 mg twice a week		Corticosteroids	Combined		10	Survived	None
	Allopurinol	TEN	20	M		1	Etanercept	25 mg twice a week		Corticosteroids	Combined		12	Survived	None
	Lamotrigine	TEN	19	F		4	Etanercept	25 mg twice a week		Corticosteroids	Combined		13	Survived	None
	Nsaids	TEN	29	F		3	Etanercept	25 mg twice a week		Corticosteroids	Combined		27	Survived	None
Bakir	Pfizer COVID-19 vaccine	TEN	49	F	30	2	Etanercept	Two doses of 50 mg/ml	1			22		Survived	None
Chahal	Meningococcal B vaccine	TEN	19	F	80	3.2	Etanercept	50 mg/ml one-time infusion	3	Supportive therapy	Combined	3	7	Survived	
Choi	Trimethoprim-sulfamethoxazole	TEN	46	M	90	3	Etanercept	Two doses of 50 mg/ml	5	Corticosteroids	Combined	15	23	Survived	

	methoxazole							mg/ml							
Coulombe	Carbamazepine	TEN	17	M	45	1	Etanercept	50 mg/ml one-time infusion	1	Corticosteroids	Combined	12	14	Survived	None
Didona	Rituximab	TEN	60	M	30	3	Etanercept	50 mg/ml one-time infusion		Corticosteroids	Combined			Survived	
Dreyer	Levofloxacin	TEN			50	3	Etanercept	50 mg/ml one-time infusion		IVIG	Combined	7		Survived	
	Trimethoprim/sulfa methoxazole	TEN			80	2	Etanercept	50 mg/ml one-time infusion				6		Survived	
	Unknown	TEN			70	2	Etanercept	50 mg/ml one-time infusion				3		Survived	
	Trimethoprim/sulfa methoxazole	TEN			35	3	Etanercept	50 mg/ml one-time infusion				NK		Survived	
	Trimethoprim/sulfa methoxazole or NSAID	TEN			50	5	Etanercept	50 mg/ml one-time infusion				NK		Survived	
	Trimethoprim/sulfa methoxazole or temozolomide or aspirin	TEN			40	3	Etanercept	50 mg/ml one-time infusion				19		Survived	
Eliades	Trimethoprim/sulfa methoxazole	TEN	4	M	80		Etanercept	50 mg/ml one-time infusion	4	Supportive therapy	Combined	18	18	Survived	Persistent dry eye disease
	Acetaminophen or influenza vaccine	TEN	7	F	80		Etanercept	50 mg/ml two dose	4	Supportive therapy	Combined	13	20	Survived	Persistent dry eye disease, trichiasis
	Trimethoprim/sulfa methoxazole	TEN	18	F	30		Etanercept	50 mg/ml one-time infusion	1	Supportive therapy	Combined		4	Survived	
	Amoxicillin-clavul anate or mefenamic acid	TEN	7	F	50		Etanercept	50 mg/ml two dose	1	Supportive therapy	Combined	10	23	Survived	Trichiasis, excessive tearing
Estébanez	Levetiracetam	TEN	8	M	30		Etanercept	0.8 mg/kg one-time infusion. A second dose of 25 mg was given one week later	3	Corticosteroids + IVIG	After	16		Survived	Bilateral ulcerative keratoconjunctivitis
Famularo	Ciprofloxacin	TEN	59	M	60		Etanercept	25 mg two dose, every other day	4	Corticosteroids	After	6		Death	
Faris	Sulfamethoxazole/t	TEN	71	F	90		Etanercept	50 mg/ml	8	Corticosteroids				Death (day 2)	



	rimethoprim							one-time infusion						after etanercept)	
		TEN	74	F	90		Etanercept	50 mg/ml one-time infusion	8	Antibiotic	After			Death (day 16 after admission)	
	Sulfamethoxazole/t rimethoprim	TEN	40	F	40		Etanercept	50 mg/ml one-time infusion	3	Corticosteroids				Death (day 11 after admission)	
Frederiks	Lamotrigine	TEN	24	F	40	1	Etanercept	50 mg/ml one-time infusion	4	Corticosteroids + ivig + antibiotic	Combined		42	Survived	Aspiration pneumonia, bacteraemia, symblepharon
	Amoxicillin	TEN	46	F	50	1	Etanercept	50 mg/ml one-time infusion	1	Corticosteroids + ivig + antibiotic	Combined		31	Survived	Symblepharon, ocular vzv, deranged liver function tests
	Ibuprofen	TEN	51	M	50	3	Etanercept	50 mg/ml one-time infusion	1	Corticosteroids	Combined		37	Survived	AMT failure requiring further surgery, UTI, hypomagnesaemia
	Acetazolamide	TEN	68	M	90	4	Etanercept	50 mg/ml one-time infusion	1	Corticosteroids + ivig + antibiotic	Combined		14	Death (day 14 after admission)	Secondary hlh; multi-organ failure; gastrointestinal bleed
Gubinelli	Phenobarbital-induced	TEN	59	F			Etanercept	25 mg/day twice (once every other day)	3	Supportive therapy + Corticosteroids	Combined	20		Survived	
Lee	Mefenamic acid and amoxicillin for a dental procedure	TEN	32	M	40	1	Etanercept	50 mg and 25 mg on the 3rd and 5th day of hospitalization	3	Corticosteroids	After	14	14	Survived	None
Maximova		TEN	21	F	50		Etanercept	25 mg one-time infusion	34	Corticosteroids + IVIG	Combined	11		Survived	
Natsis		TEN	20	F	60		Etanercept	50 mg one-time infusion					30	Survived	
Osawa	Apalutamide for metastatic prostate cancer	TEN	77	M		4	Etanercept	50 mg once a week for 6 dose	43	Corticosteroids + IVIG + mpsl pulse therapy + Plasmapheresis	Combined			Survived	
Paradisi	Carbamazepine	TEN	57	F		6	Etanercept	50 mg one-time	3	Supportive therapy		12		Survived	None

								infusion							
	Ofloxacin	TEN	70	M		3	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Lansoprazole, azathioprine	TEN	28	F		2	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Methylprednisolone	TEN	62	F		3	Etanercept	50 mg one-time infusion	3	Supportive therapy		12		Survived	None
	Carbamazepine	TEN	73	M		4	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Carbamazepine	TEN	78	M		5	Etanercept	50 mg one-time infusion	3	Supportive therapy		7		Survived	None
	Phytotherapy product	TEN	72	F		2	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Carbamazepine	TEN	50	F		6	Etanercept	50 mg one-time infusion	3	Supportive therapy		20		Survived	None
	Carbamazepine	TEN	71	M		2	Etanercept	50 mg one-time infusion	3	Supportive therapy		9		Survived	None
	Diclofenac	TEN	55	F		3	Etanercept	50 mg one-time infusion	3	Supportive therapy		9		Survived	None
Paradisi	Mirtazapine	TEN	68	F		5	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Carbamazepine	TEN	71	F		4	Etanercept	50 mg one-time infusion	3	Supportive therapy		21		Survived	None
	Naproxen	TEN	67	M		6	Etanercept	50 mg one-time infusion	3	Supportive therapy		9		Survived	None
	Ciprofloxacin	TEN	74	M		5	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Allopurinol	TEN	55	F		3	Etanercept	50 mg one-time infusion	3	Supportive therapy		7		Survived	None
	Diclofenac	TEN	57	F		3	Etanercept	50 mg one-time infusion	3	Supportive therapy		7		Survived	None
	Ciprofloxacin	TEN	79	F		4	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Diclofenac	TEN	90	M		6	Etanercept	50 mg one-time infusion	3	Supportive therapy		6		Death	
	Cephalosporin	TEN	81	M		4	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Cephalosporin	TEN	81	M		5	Etanercept	50 mg one-time	3	Supportive therapy		8		Survived	None

								infusion							
	Rituximab	TEN	51	M		4	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Rituximab	TEN	61	F		5	Etanercept	50 mg one-time infusion	3	Supportive therapy		10		Survived	None
	Ibuprofen	TEN	77	F		4	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
	Paracetamol	TEN	19	M		2	Etanercept	50 mg one-time infusion	3	Supportive therapy		9		Survived	None
	Cephalosporin	TEN	27	M		3	Etanercept	50 mg one-time infusion	3	Supportive therapy		9		Survived	None
	Allopurinol	TEN	90	M		6	Etanercept	50 mg one-time infusion	3	Supportive therapy		7		Death	
	Azathioprine	TEN	81	F		4	Etanercept	50 mg one-time infusion	3	Supportive therapy		8		Survived	None
Shen	Human herpesvirus 7	TEN	12	F	60		Etanercept	Two dose 25 mg	6	Corticosteroids	After	21	23	Survived	Pterygium and postinflammatory hyperpigmentation.
Sibbald	Ibuprofen/acetaminophen	TEN	2	M		4	Etanercept	0.4 mg/kg on days 6 + 8	6	IVIG + corticosteroids	Combined		52	Survived	In hospital complications: infections (cutaneous, urinary tract); sequelae after discharge: persistent skin dyspigmentation
Torres - Navarro	Ibuprofen	TEN	30	F	95	2	Etanercept	50 mg in a single dose	5				19	Survived	
Zander	Sulfamethoxazole-trimethoprim for epididymitis	TEN	13	M	50		Etanercept	Two 50 mg doses four days apart	2	Corticosteroids + Supportive therapy	Combined	5	13	Survived	None
Zhang	Alamotrigine	TEN	50	F	70	3	Etanercept	50 mg/ml one-time infusion	8	Corticosteroids + IVIG				Death	