INT-012

An analysis on safety profile of biologic agents in pediatric patients with juvenile rheumatoid arthritis

J.Y. Choi[1], A.H. Jung[1], S.H. Jung[1], H.J. Hahn[1], J.G.Kim[2], W.G.Shin[3]

[1]Seoul National University Hospital, Pharmacy, Seoul, Korea- South.
[2]Seoul National University Hospital, Pediatrics, Seoul, Korea- South.
[3]Seoul National University, Pharmacy, Seoul, Korea- South.

Background & Objectives

1. Concerns for biologic therapy for JRA include an increased risk of infections, particularly opportunistic or *Mycobacterium* infections, autoimmune syndrome, infusion or injection-site reactions, neuropsychiatric adverse events(AEs)
2. We can rarely get the safety profile of biologic therapy in JRA patients under 18 years old. The goal of this study is to provide data on safety of biologic agents in pediatric patients with JRA and find risk factors for adverse events.

Methods

1. Retrospective EMR analysis
   1) 2004.4-2013.6
   2) Seoul National University Hospital
   3) Pediatric patients(<18YO) with juvenile rheumatoid arthritis
   4) Etanercept, Infliximab
2. Definition of Adverse events
   1) Infection: tuberculosis, herpes zoster, pneumonia, upper respiratory infection, chicken pox
   2) Injection site reaction: Injection site rash, itching, pain
   3) Infusion reaction: rash, urticaria, itching, dyspnea, fever
   4) Neuropsychiatric manifestation: headache, depression, anxiety, seizure, tremor, fatigue
   5) Autoimmune phenomena: lupus-like syndrome, uveitis, demyelinating disease, psoriasis
   6) Malignancy: lymphoma
3. Data analysis
   1) Casualty assessment: WHO-UMC Criteria
   2) Severity assessment: Hartwig's Severity Assessmet scale
   3) Correlation analysis: Logistic regression analysis
   4) Risk factor: age, sex, number of DMARDs, dosage of methotrexate and prednisolone

Results

1. Patients demographics

	Etanercept	Infliximab
N	83	6
Female No(%)	44(53)	3(50)
Median age (years)	15	18
Median age to start biologic therapy (years)	10.4	13.7
Median JRA disease duration (days)	2608	3823
Median duration of biologic therapy (days)	1447	172
Dosage mean(per kg)	0.5mg	2.9mg

2. Biologic therapy population

	n	1st switch	2nd switch
Etanercept only	74		
Etanercept-> Infliximab	1	treatment failure	
Etanercept-> Infliximab-> Etanercept	4	3: treatment failure 1: insurance limitation	3: treatment failure 1: Insurance limitation
Etanercept-> Infliximab -> Anakinra	1	treatment failure	treatment failure Adverse events(dyspnea, rash)
Etanercept-> Adalimumab-> Etanercept	1	treatment failure	treatment failure
Etanercept-> Abatacept	1	treatment failure	
Etanercept-> Anakinra	1	treatment failure	
Total	83		

3. DMARDs treatment population

	Etanercept	Infliximab
None	6(7.2%)	-
Methotrexate	57(68.7%)	4(66.7%)
Methotrexate + Sulfasalazine	17(20.5%)	1(16.7%)
Methotrexate + Hydroxychloroquine	3(3.6%)	-
Methotrexate + Sulfasalazine	-	1(16.7%)
Cyclophosphamide	-	-
Total	83	6

4. Steroid and methotrexate treatment population

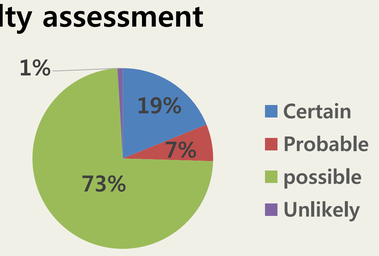
	Etanercept	Infliximab
No of patients treated with steroid(%)	33(39.8%)	2(33.3%)
No of patients treated with prednisolone	32	1
Prednisolone dose mean(mg/kg/day)	0.34	0.12
No of patients treated with deflazacort	1	1
Deflazacort dose mean(mg/kg/day)	0.05	0.15
No of patients treated with methotrexate(%)	77(92.8%)	6(100%)
Methotrexate dose mean(mg/kg/week)	0.26	0.3

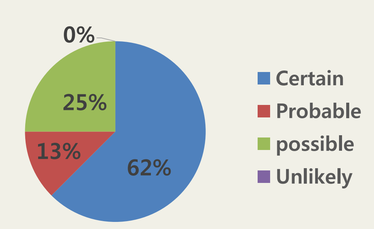
Results

5. Adverse events observed in the study population

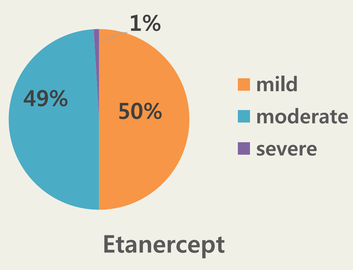
Adverse Event	Etanercept (328 Patient treatment years)			Infliximab (4 Patient treatment years)			Total (332 Patient treatment years)		
	No of AEs	No of patients	No of AEs/Patient year	No of AEs	No of patients	No of AEs/Patient year	No of AEs	No of patients	No of AEs/Patient year
Infection	42 (39.6%)	30 (36.1%)	0.128	2 (25%)	2 (33%)	0.476	44 (37%)	30 (36.1%)	0.132
URI	36 (34%)	28 (33.7%)	0.110	1 (12.5%)	1 (16.7%)	0.238	37 (31.1%)	28 (33.7%)	0.111
Pneumonia	3 (2.8%)	2 (2.4%)	0.009				3 (2.5%)	2 (2.4%)	0.009
Chicken pox	1 (0.9%)	1 (1.2%)	0.003	1 (12.5%)	1 (16.7%)	0.238	2 (1.7%)	2 (1.2%)	0.006
Herpes zoster	2 (1.9%)	2 (1.2%)	0.006				2 (1.7%)	2 (1.2%)	0.006
Injection site reaction	17 (16%)	17 (20.5%)	0.052				17 (14.9%)	17 (20.5%)	0.051
Neuropscychiatric symptom	22 (20.8%)	22 (26.5%)	0.067				22 (19.2%)	22 (26.5%)	0.267
Headache	13 (12.3%)	13 (15.7%)	0.040				13 (11.4%)	13 (15.7%)	0.039
numbness	2 (1.9%)	2 (2.4%)	0.006				2 (1.7%)	2 (2.4%)	0.006
Hearing impairment	2 (1.9%)	2 (2.4%)	0.006				2 (1.7%)	2 (2.4%)	0.006
Seizure	1 (0.9%)	1 (1.2%)	0.003				1 (0.8%)	1 (1.2%)	0.003
Tremor	1 (0.9%)	1 (1.2%)	0.003				1 (0.8%)	1 (1.2%)	0.003
Fatigue	1 (0.9%)	1 (1.2%)	0.003				1 (0.8%)	1 (1.2%)	0.003
Syncope	2 (1.9%)	2 (2.4%)	0.006				2 (1.7%)	2 (2.4%)	0.006
Generalized skin reaction	7 (6.6%)	7 (8.4%)	0.021				7 (6.1%)	7 (8.4%)	0.021
Infusion reaction	0	0	0	6 (75%)	4 (66.7%)	1.428	6 (5.0%)	4 (4.7%)	0.018
Uveitis	5 (4.7%)	5 (6.0%)	0.015				5 (4.2%)	5 (6.0%)	0.015
Bleeding	2 (1.9%)	2 (2.4%)	0.006				2 (1.7%)	2 (2.4%)	0.006
Fever	6 (5.7%)	6 (7.2%)	0.018				6 (5%)	6 (7.2%)	0.018
GI symptom	5 (4.7%)	5 (6.0%)	0.015				5 (4.2%)	5 (6.0%)	0.015
Dyspnea	1 (0.9%)	1 (1.2%)	0.003				1 (0.8%)	1 (1.2%)	0.003
LFT 상승	2 (1.7%)	2 (2.3%)	0.006				2 (1.7%)	2 (2.3%)	0.006
Total ADR	106	52	0.32	8	5	1.9	114	53	0.34

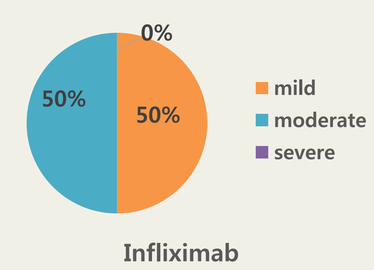
6. Casualty assessment





7. Severity assessment





8. Correlation between infectious AEs vs risk factors in Etanercept group

Characteristic	No of patients with infection	Univariable Analysis OR (95% CI)	*P* Value	Multivariable Analysis OR (95% CI)	*P* Value
Age to start biologic therapy		0.9(0.832-0.974)	0.009		
Sex					
Female	27	1 [Reference]			
Male	3	0.248(0.100-0.614)	0.003	0.402(0.141-1.148)	0.089
DMARD, No.					
0	4	1 [Reference]			
1	8	0.929(0.319-2.700)	0.892		
2	18	1.083(0.309-3.802)	0.901		
Duration, days		1.001(1.000-1.001)	0.001	1.001(1.000-1.001)	0.022
Methotrexate Dose(mg/kg/wk)		0.554(0.056-5.446)	0.612		
Etanercept Dose(mg/kg/wk)		1.216(0.753-1.963)	0.424		
Steroid					
With steroid	16	1 [Reference]			
Without steroid	14	2.033(0.971-4.257)	0.060		
Dose(mg/kg/day)		7.786(1.464-41.399)	0.016	9.674(1.396-67.026)	0.022

Conclusions

1. Most of AEs were evaluated as mild to moderate.
2. Steroid dose per weight(kg) was significantly associated with infections occurred in patients treated with etanercept (P=0.022). It is necessary to monitor symptoms of infections including fever and sore throat especially in patients treated with etanercept and steroids.
3. Injection site reactions of etanercept were reported more often in patients who treated with syringe type compared to vial type(55% vs 9.5%).
4. It is necessary to educate and monitor patients treated with infliximab because infusion reactions observed in infliximab might be life-threatening and occur after a few days after infusion.

NO conflict of interest