Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2021.39.006244

Extensive Proof-of-Concept Studies in TNF-Alpha Antagonists might be Responsible for A Delay of Patient Access in Pediatric Rheumatology

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ARTICLE INFO

Received: September 21, 2021

Published: September 28, 2021

Citation: Nalân Utku, Peter Schlattmann, Glyn Steventon, Birka Lehmann, Jürgen Brunner. Extensive Proof-of-Concept Studies in TNF-Alpha Antagonists might be Responsible for A Delay of Patient Access in Pediatric Rheumatology. Biomed J Sci & Tech Res 39(1)-2021. BJSTR. MS.ID.006244.

Keyword: Pediatrics; Trials; Approval

ABSTRACT

Background: Many medicinal products have been given to children without regulatory approval. The European and US regulatory authorities introduced legislation to improve the route to market for therapeutics for use in children in 2007. Thus, new drugs have to be clinically tested in children to gain approval in adults, unless predicted to be unsafe, ineffective or not needed in children.

Main body: Our meta-analysis focuses on the use of immune-modulatory biologics. It compares data obtained from studies using etanercept, infliximab and adalimumab in juvenile idiopathic arthritis (JIA) and adult rheumatoid arthritis (RA) and argues that efficacy and safety in children could be extrapolated from the data in a corresponding adult disease, although, for chimeric or pegylated biologics, PK/PD parameter analysis would need to be investigated before selecting the effective dose in children.

Conclusion: Use of this model has potential to enhance the clinical use of pediatric drugs, tailored to age, weight, and physiological development.

Key Messages:

a) Supplementary and extensive pediatric trials delay marketing approval for effective medicines for children

b) Adult trial results in RA together with PK studies in children are likely to be sufficient for marketing approval of TNF-α inhibitors for JIA

Introduction

In order to improve the route to market for approved pediatric therapeutics, the current Pediatric Regulation in the EU and the Food and Drug Administration (FDA) Amendments Act (FDAAA) were both adopted in 2007. These include incentives for the pharmaceutical industry to perform pediatric clinical studies, for example granting an extended patent protection time or marketing exclusivity for orphan medicinal products for a limited period. Between 2007 and 2013, the European Medicines Agency (EMA) and its Pediatric Committee assessed more than 600 pediatric investigation plans (PIPs) with an aim to provide data on the

efficacy and safety of medicines for diseases of children. After almost a decade of experience of PIPs, it seemed important to evaluate the usability of data derived from clinical trials for new medicinal products in children for marketing authorization. This is particularly important in order to understand the need for, and extent of, clinical studies for new drugs in children in the future. The aim of this study is to evaluate whether proof-of-concept clinical trials need to be carried out at the existing rate and frequency, and whether data to support the use of new drugs in children can be extrapolated from adult trials of equivalent indications with focus on rheumatology. This evaluation should help to outline new guidance for clinical trials for new drugs in children to prevent unnecessary extensive trials of 'me-too' drugs.

Strategy

The review compared the effects of immune-modulatory drugs in adults and children, selected using the following criteria:

a) Biologics in the same class to treat arthritis

b) Clinically tested for the same or a similar indication in children and adults

c) Subject to a PIP in children and approved for use in adults.

Drugs selected for this review are biologics targeting TNF-α including adalimumab, etanercept, golimumab, and infliximab.

TNF-α Inhibitors Tested in Adults and Children

Etanercept (Enbrel, Pfizer) is a soluble decoy receptor for TNF. It was the first TNF-α inhibitor launched for treatment of RA. The drug was FDA-approved in November 1998, and by the EMA in February 2000. It is approved for the treatment of RA, JIA, psoriatic arthritis, plaque psoriasis and ankylosing spondylitis [1] as the first biologic to treat JIA. Adalimumab (Humira, Abbot [now: AbbVie]) is a monoclonal anti-TNF-α inhibitor. It was the first fully human IgG1 protein to be approved by the FDA in December 2002. It was approved by the EMA in September 2003. Adalimumab is indicated for the treatment of RA, JIA, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis and ulcerative colitis [2]. It was approved for JIA in 2008. Golimumab (Simponi, Janssen Biotech) is a human anti-TNFα IgG1κ monoclonal antibody. Golimumab was approved in US and Canada as a treatment for RA, psoriatic arthritis, and spondylitis, and is undergoing regulatory review in the EU [3] for these indications. Golimumab missed the primary endpoint in JIA. Infliximab (Remicade, Janssen Biotech) is a chimeric monoclonal antibody directed against TNF-α which induces apoptosis in TNF-α-receptor + cells. Infliximab is only approved for RA. It failed to meet primary endpoint in JIA and therefore has not been approved by the FDA in children for JIA. A waiver for the PIP was agreed in the EU. Infliximab is used off label in JIA as it has not been approved for this indication.

Search Strategy

The search was focused on RA in adults and on JIA, prescribing information, clinical trials websites and the FDA and EMA websites in order to identify relevant study information [4-16]. Keywords employed for the searches: Adalimumab, etanercept, golimumab, infliximab; juvenile idiopathic arthritis, JIA, juvenile rheumatoid arthritis, JRA, systemic juvenile idiopathic arthritis, SJIA, polyarticular juvenile idiopathic arthritis, PJIA; pediatrics, children, adults; tumor necrosis factor inhibitors, TNF-α, phase III.

Statistical Meta-Analysis

Statistical analysis was performed using a logistic regression with random effects. The primary outcomes are the ACR50 and ACR70. The dependent variable is the number of patients who reach ACR50 or ACR70 based on the total number of patients treated. Independent variables are treatment, age group (children vs. adults) and time. Treatment is a categorical variable, which compares several treatment regimens with placebo. As not every study has a placebo control arm, we therefore performed an implicit comparison with placebo. The variance of the random effects takes the variability between studies into account. Moreover, as several time points within a study are considered, this model takes also within study correlation into account. The comparison aimed to reveal different treatment responses in children compared to adults. This comparison is quantified using the odds ratio with a 95% confidence interval. Additionally, the response probability adjusted for treatment and time is given with a 95% confidence interval for each group. Calculations were performed with prpc glimmix, SAS 9.4.

Results

A comparative analysis using clinical and pharmacokinetic data was performed, based on data obtained from pivotal studies of biologics for the treatment of inflammation in children vs. adults and evaluated in terms of efficacy, safety and dose used. In total, one or two pivotal pediatric trials, and four to seven pivotal studies in adults for all biologics were identified. All drugs were given as either monotherapy or in combination with methotrexate, and either placebo-controlled or without control. The following section summarizes results (Tables 1-6) obtained from meta-analyses.

Table 1a: Comparison of clinical trials with etanercept in children and adults.

	CHILDREN		**ADULTS**							
Study Characteristics	**Lovell, 2000**		**Moreland, 1999**		**Weinblatt, 1999**		**Bathon, 2000**		**Klareskog, 2004**	
	JIA-I		Study I		Study II		Study III		Study IV	
Dosage	- 0.4 mg/Kg of body weight subcutaneously twice a week (max. 25 mg per dose) - Placebo		- 25 mg subcutaneous injections twice a week - 10mg subcutaneous injections twice a week - Placebo		- 25 mg subcutaneous injection twice a weekly + MTX (12.5-25 mg/wk) - Placebo + MTX (12.5-25 mg/wk)		- 25 mg subcutaneous injection twice a weekly - 10 mg subcutaneous injection twice a weekly - Placebo + 7.5mg MTX weekly		- 25 mg subcutaneously twice a week - 25 mg subcutaneously twice a week + MTX (up to 20 mg weekly) - MTX (up to 20 mg weekly)	
DMARDs during study	Not permitted		Not permitted		Not permitted		Not permitted		Not permitted	
Study duration	- open-label study: 3 months - double-blind study: 4 months (or until flare)		6 months		6 months		12 months		6 months	
ACR results	Week 12(OL), Week 16 (DB)		Week 24		Week 24		Week 48		Week 24	
ACR50 [%]	OL study	64 vs. Nd	10 mg	24 vs. 5	39 vs. 3		10 mg	32 vs. 43	25mg	a 41 vs. 41
drug vs. placebo	DB study	72 vs. 23	25 mg	40 vs. 5			25 mg	49 vs. 43	25 mg + MTX	a 59 vs. 41
ACR70 [%]	OL study	36 vs. Nd	10 mg	9 vs. 1	15 vs. 0		10 mg	16 vs. 22	25mg	a 17 vs. 15
drug vs. placebo	DB study	44 vs. 19	25 mg	15 vs. 1			25 mg	25 vs. 22	25 mg + MTX	a 36 vs. 15
AEs and SAEs										
Most frequently	No. (%) of patients		% Of adverse events		% Of patients		No. (%) of patients		No. (%) of patients	
Injection site reaction	OL (39); DB (1); DB plcbo. (1)		25 mg	49	25 mg	42	25 mg	77 (37)	25mg	46 (21)
			10 mg	43	placebo	7	10 mg	63 (30)	25 mg + MTX	23 (10)
			placebo	13			placebo	16 (7)	placebo	4 (2)
Headache	OL (20); n.a. ; n.a.		25 mg	14	25 mg	20	25 mg	46 (22)	25mg	34 (15)
			10 mg	20	placebo	17	10 mg	52 (25)	25 mg + MTX	34 (15)
			placebo	10			placebo	59 (27)	placebo	31 (14)
Upper respiratory tract infection	OL (35); n.a. ; n.a.		25 mg	33			25 mg	72 (35)		
			10 mg	29	n.a.		10 mg	57 (27)	n.a.	
			placebo	16			placebo	84 (39)		
Rhinitis	OL (16); n.a. ; n.a.		25 mg	10	25 mg	14	25 mg	31 (15)		
			10 mg	12	placebo	3	10 mg	36 (17)	n.a.	
			placebo	11			placebo	30 (14)		
Nausea	OL (12); n.a. ; n.a.		n.a.		25 mg	10	25 mg	35 (17)	25mg	22 (10)
					placebo	23	10 mg	29 (14)	25 mg + MTX	55 (24)
							placebo	62 (29)	placebo	73 (32)
Rash	OL (10); n.a. ; n.a.		n.a.		n.a.		25 mg	50 (23)	25mg	16 (7)
							10 mg	33 (16)	25 mg + MTX	23 (10)
							placebo	50 (23)	placebo	21 (9)

Abbreviations:
n.a: not available
OL: open label
DB: double-blind
MTX: Methotrexate

Table 1b: Pharmacology data of clinical trials with etanercept in children and adults.

	CHILDREN (JIA) (4 to 17 years of age)	ADULTS (RA)	
Pharmacology	Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-α and TNF-beta (lymphotoxin α [LT-α]) to cell surface TNFRs, rendering TNF biologically inactive.		
PD	Etanercept can modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (e.g., E-selectin, and to a lesser extent, intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (e.g., IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin).		
	The dose is derived from the outcomes of controlled pivotal studies. Enbrel 25 mg administered twice weekly as a subcutaneous injection, is the recommended dose for optimal therapeutic response in rheumatoid arthritis; alternatively 50 mg administered once weekly was been shown to be safe and effective in a subsequent clinical study. 25 mg administered once weekly gives a slower response and maybe less effective.		
Data Source	Lovell, 2000	Moreland 1999	Bathon 2000
Hematologic Events		No abnormalities in laboratory values in the etanercept groups. C-reactive protein level, erythrocyte sedimentation rate, platelet count, albumin level, and leukocyte count returned to normal.	Patients taking MTX more likely to have low peripheral-blood lymphocyte counts («1400 per cubic millimetre) than those taking 25 mg etanercept (79% vs. 56%). Non-recurrent neutropenia more frequently in the group receiving 25 mg etanercept than in the MTX group (16% vs. 8%). Five patients (2 in MTX group, 1 in the 10 mg etanercept, and 2 in the 25 mg etanercept group) had transient grade 3 neutropenia (at least 500 but fewer than 1000 neutrophils per cubic millimetre).
Immunology	No patient had persistent elevations in autoantibodies or had signs or symptoms of another autoimmune disease. Two patients positive for non-neutralizing antibody to etanercept.	Non-neutralizing antibodies to etanercept were detected in one patient. Regarding to the levels of antinuclear antibodies and anticardiolipin antibodies, a small number of patients in each group shifted from positive to negative or from negative to positive test results, with no significant differences between the groups.	Less than 3% of etanercept-treated patients were positive intermittently on tests for serum non-neutralizing antibodies against etanercept, and the positive tests were not associated with a decrease in the clinical response or adverse effects.

PK										
Data Source	PI	Yim 2005		PI and EMA			Zhou 2004		Zhou 2005	
	0.4 mg/kg twice weekly (max. 50 mg/week) for up to 18 weeks.	The pharmacokinetic data were obtained from the clinical trial of etanercept in paediatric patients with severe polyarticular JRA		Study I: 25 mg single sc injection in RA patients	Study II: 50 mg once weekly or 25 mg twice weekly in RA patients.		The single-dose and multiple-dose pharmacokinetics of etanercept in patients with RA for 24 weeks. 25 mg etanercept dose sc, followed in 3 weeks by 25 mg twice weekly for 6 months		The single-dose and multiple-dose pharmacokinetics of etanercept in patients with RA for 24 weeks. 25 mg etanercept dose sc, followed in 3 weeks by 25 mg twice weekly for 6 months	
					50 mg	25 mg			Single-Dose (n=25)	Multiple-Dose (n=23)
mean serum concentration [µg/mL]	2.1 (range of 0.7 to 4.3)									2.7 (range of 1.4 to 16.7)
Absorption										
ka [1/h]							0.028			
$C_{ss,\ trough}$ [µg/mL]		0.4 mg/kg twice weekly (mean±SD)	0.8 mg/kg once weekly				Eta:	Eta+MTX:		

		1.92 ± 1.09	(mean±SD)				2.0 ± 0.1		2.26 ± 0.08		
			1.58 ± 1.07								
C_{max} [µg/mL]		2.62 ± 1.23	2.92 ± 1.41	(mean±SD)	2.4±1.5	2.6±1.2				1.072 ± 0.635	2.4 ± 0.99
				1.1 ± 0.6							
C_{min} [µg/mL]					1.2±0.7	1.4±0.7					
T_{max} [h]				(mean±SD)						69.2 ± 33.8	32.1 ± 27.3
				69 ± 34							
average absolute bioavailability [%]				76			62.6				
partial AUC [µg·h/mL]					297±166	316±135				a201.7 ± 94.3	a143.6 ± 57.2
Distribution											
V_{ss} [L]		7.88		10.4 (for a 70 kg subject)							
V_c [L]							5.97				
V_p [L]							2.05				
Elimination											
C_l [mL/h]		(Calculated for a subject with BSA 1.071 m2 and body weight 30.8 kg (median values)):		(mean±SD)			72				
		Female: 57.6 / Male: 77.2		160 ± 80							
Q [mL/h]							65				
half-life [days]		(calculated for a subject weighing 30.8 kg):		(mean±SD)						102.3 ± 30.1	93.7 ± 18.6
		Female: ~4 / Male: ~3		102 ± 30							

Abbreviations:

PD: Pharmacodynamics

PK: Pharmacokinetics

ka: First-order absorption rate constant

$C_{ss, trough}$: steady-state trough concentration

C_{max}: Maximum serum concentration

C_{min}: Minimum serum concentration

T_{max}: Time to reach the maximum concentration

V_{ss}: Distribution volume

V_c: Volume of distribution in the central compartment

V_p: Volume of distribution in the peripheral compartment

C_L: Clearance

Q: Intercompartment clearance

Table 2a: Comparison of clinical trials with adalimumab in children and adults.

	CHILDREN				ADULTS							
Study Characteristics	Lovell, 2008			Kingsbury, 2014		Weinblatt, 2003		Van de Putte, 2004		Keystone, 2004		Furst, 2003
	PJIA-I			PJIA-II		RA-I		RA-II		RA-III		RA-IV
Dosage	- Subcutaneous injection 24 mg/ m^2 body-surface area (max. 40 mg) ± MTX - Placebo ± MTX			- Subcutaneous injection 24 mg/m^2 every other week (max. 20 mg/dose) ± MTX		- Subcutaneous injections 20 mg, 40 mg, or 80 mg every other week + MTX. - Placebo + MTX		- Subcutaneous injections 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly, or placebo.		- Subcutaneous injections at 40 mg every other week + MTX or 20 mg every week + MTX - Placebo + MTX		- Subcutaneous injections 40 mg every other week. - Placebo
NSAIDs and/or corticosteroids	Permitted			Permitted; No DMARDs		Permitted; No DMARDs		Allowed before the study. No DMARDs		Permitted; No DMARDs		Permitted; DMARDs permitted
Study duration	- open label study: 16 weeks			Up to 120 weeks		24 weeks		26 weeks		52 weeks		24 weeks
	- double blind study: 32 weeks. (Total 48 weeks)			open-label study								
ACR results	Week 16(OL), Week 48 (DB)a			Observed analysis at weeks 12, 24, 60, and 96		Week 24		Week 26		Week 24 and week 52		Week 24
ACR50 [%]	OL +MTX	91 vs. n.a.		Week 12	90	20 mg	22 vs. 5	20mg every other week.	20 vs. 9	w24 / 40mg	81 vs. 19	28.9 vs. 11.3
drug vs. placebo	OL – MTX	64 vs. n.a.		Week 24	83	40 mg	37 vs. 5	20mg wkly.	23 vs. 9	w24 / 20mg	87 vs. 19	
	DB +MTX	63 vs. 38		Week 60	80	80 mg	31 vs. 5	40mg e.o.w.	25 vs. 9	w52 / 40mg	86 vs. 19	
	DB -MTX	53 vs. 32		Week 96	92			40mg wkly.	36 vs. 9	w52 / 20mg	80 vs. 19	
ACR70 [%]	OL +MTX	71 vs. n.a.		Week 12	61	20 mg	7 vs. 3	20mg every other week.	9 vs. 2	w24 / 40mg	43 vs. 5	14.8 vs. 3.5
drug vs. placebo	OL – MTX	46 vs. n.a.		Week 24	73	40 mg	18 vs. 3	20mg wkly.	11 vs. 2	w24 / 20mg	37 vs. 5	
	DB +MTX	63 vs. 27		Week 60	70	80 mg	14 vs. 3	40mg every other week	14 vs. 2	w52 / 40mg	48 vs. 9	
	DB -MTX	47 vs. 29		Week 96	77			40mg wkly.	19 vs. 2	w52 / 20mg	44 vs. 9	
AEs and AEs												
Most frequently	No. (%) of patients			No. (%) of patients		No. (%) of patients		No. (%) of patients		No. (%) of patients		No. (%) of patients
Injection site reaction	Placebo+MTX	57 (3.8)		4 (12.5)		Placebo	0	Placebo	1 (0.9)	Placebo	48 (24)	Placebo
	Placebo-MTX	20 (1.9)				20 mg	3 (4.3)	Ada groups	46(10.6)	20 mg	47 (22.2)	40 mg
	OL + MTX	142(5.2)				40 mg	1 (1.5)			40 mg	54 (26.1)	
	OL –MTX	166(5.7)				80 mg	8 (11)					
	DB +MTX	73 (4.0)										
	DB -MTX	71 (4.9)										

Upper respiratory tract infection	Placebo+MTX	5 (0.3)	6 (19)	Placebo	6 (9.7)	Placebo	n.a.	Placebo	27 (13.5)	Placebo
	Placebo-MTX	6 (0.6)		20 mg	14 (20.3)	Ada groups	n.a.	20 mg	41 (19.3)	40 mg
	OL + MTX	9 (0.3)		40 mg	10 (14.9)			40 mg	41 (19.8)	
	OL –MTX	11 (0.4)		80 mg	16 (21.9)					
	DB +MTX	6 (0.3)								
	DB -MTX	6 (0.4)								

Table 2b: Pharmacology data of clinical trials with adalimumab in children and adults.

	CHILDREN (JIA) (4 to 17 years of age)		**ADULTS (RA)**			
Pharmacology	Blocks interaction of human TNF-α with receptors and modulates biological responses induced or regulated by TNF (changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 1-2 X 10-10M). It does not bind or inactivate lymphotoxin (TNF-beta).					
PD	- Decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRPJ and erythrocyte sedimentation rate (ESRJ) and serum cytokines (IL-6).					
	- Decrease in serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction.					
Data Source	Lovell 2008	Kingsbury 2014	Weinblatt 2003	Van de Putte 2004	Keystone 2004	Furst 2003
Hematologic Events			The hematocrit value, haemoglobin concentration, and percentage of lymphocytes showed increases, and the platelet count showed a decrease.		Adalimumab therapy was associated with statistically significant decreases (compared with baseline values) in the mean white blood cell count, platelet count, and neutrophil percentage, as well as statistically significant increases (compared with baseline values) in the mean haemoglobin concentration, hematocrit, and lymphocyte percentage (data not shown), with all of these indices moving toward more normal values. In the placebo group, changes in all of these parameters were of less magnitude and were not statistically significant for the platelet count and lymphocyte percentage.	Mean changes in haematology values were comparable between the adalimumab and placebo groups. Overall, the mean changes for all biochemistry variables were small and were comparable for patients treated with adalimumab and placebo.

Immunology	16% patients had at least one positive test for anti-adalimumab antibody during the open-label and double-blind phases: 6% receiving MTX and 26% not receiving MTX. Development of anti-adalimumab antibody did not lead to a greater rate of discontinuation of the study drug.		Among the 15 patients who had samples for pharmacokinetic analysis, only one patient (6.7 %) developed AAA+ during the 24 weeks that were evaluated.			Over the course of the study, 12% of adalimumab treated patients tested positive for antibodies against adalimumab; however, there were no differences in the pattern or frequency of adverse events between patients with or without these antibodies	Two patients in the group receiving adalimumab 40 mg every other week, 1 patient in the group receiving adalimumab 20 mg weekly, and 1 patient in the placebo group were positive for anti-adalimumab antibodies on at least 1 occasion.	
PK								
Data Source	PI		Kingsbury 2014			PI		Nestorov 2005
						In RA patients receiving 40 mg HUMIRA every other week		PK data for adalimumab have been published in RA patients and are summarized in this review.
								Adalimumab is administered subcutaneously (sc) by a 40 mg uniform multiple dosing every other week.
mean serum concentration [µg/mL]	20 mg monotherapy	6.8	Monotherapy:		Ada+MTX:	monotherapy	5	5.5 ± 2.5
	20 mg + methotrexate	10.9	6			with methotrexate	8–9	
	40 mg monotherapy	6.6			7–8			
	40 mg + methotrexate	8.1						
Absorption						Single 40 mg subcutaneous injection to healthy adult subjects		
ka [1/h]								
$C_{ss,\,trough}$ [µg/mL]								
C_{max} [µg/mL]						4.7 ± 1.6		7.7 ± 3.4
$_{Cmin}$ [µg/mL]								3.8 ± 2.1
T_{max} [h]						131 ± 56		90 ± 48
average absolute bioavailability [%]						64		
$AUC_{0\text{-}T}$ [mg h/L]								1830 ± 850
Distribution								
V_{ss} [L]						4.7 to 6		
V_c [L]								
V_p [L]								
Elimination								
Cl [mL/h]	.					12		

Q [mL/h]				
half-life [days]			15	
Source: PI	- No gender-related pharmacokinetic differences were observed after correction for a patient's body weight.			
	- Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.			
	- Haematological events: Adverse reactions of the hematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA.			
	- Autoimmunity: Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome.			

Table 3a: Comparison of clinical trials with infliximab in children and adults.

	Children				**Adults**					
1. Study Characteristics	Ruperto, 2007				Maini, 1999				St Clair, 2004	
Dosage	Infusion of infliximab 3 mg/kg (+MTX) for 44 weeks or placebo for 14 weeks followed by MTX + infliximab 6mg/kg (+MTX) through week 44				Intravenous infliximab injections (3 mg/kg or 10 mg/kg, +MTX) every 4 or 8 weeks through week 30 versus placebo + MTX				Infusion of placebo (+MTX), 3 mg/kg infliximab (+MTX), or 6 mg/kg infliximab(+MTX) at weeks 0, 2, and 6, and q8w thereafter through week 46	
DMARDs, NSAIDs and/or corticosteroids during study	MTX and intraarticular corticosteroid injections allowed				MTX and NSAIDs allowed				MTX, oral corticosteroids and NSAIDs	
Study duration	44 weeks				30 weeks				54 weeks	
2. ACR Results										
					Week 30				Week 54	
ACR50		P/6mg/kg		3mg/kg	3mg/kg q8w	3mg/kg q4w	10mg/kg q8w	10mg/kg q4w	3mg/kg	6mg/kg
drug vs. placebo [n (%)]	Week 14	20/59 (33.9)		29/58 (50)	22 (27) vs.	25 (29) vs.	26 (31) vs.	21 (26) vs.	(45.6) vs. (32.1)c	(50.4) vs. (32.1)
	Week 52	78/112 (69.9)			4 (5)c	4 (5)c	4 (5)c	4 (5)c		
ACR70		P/6mg/kg		3mg/kg	3mg/kg q8w	3mg/kg q4w	10mg/kg q8w	10mg/kg q4w	3mg/kg	6mg/kg
drug vs. placebo [n (%)]	Week 14	7/59 (11.9)		13/58 (22.4)	7 (8) vs.	9 (11) vs.	15 (18) vs.	9(11) vs.	(32.5) vs. (21.2)	37.2 vs (21.2)
	Week 52	58/112 (51.8)			0 (0)c	0 (0)c	0 (0)c	0 (0)c		
4. AEs and SAEs										
Most frequently	Placebo vs. drug No [%]				Placebo vs. drug No [%]				Placebo vs. drug No [%]	
	6mg/kg		3 mg/kg		3mg/kg q8w	3mg/kg q4w	10mg/kg q8w	10mg/kg q4w	3mg/kg	6mg/kg
General disorders										
injection-site reaction	5 (8.3) vs. 10 (17.5)		5 (8.3) vs. 21 (35.0)							
Rash					4 (5%) vs. 5 (6%)	4 (5%) vs. 7 (8%)	4 (5%) vs. 14 (16%)	4 (5%) vs. 11 (14%)		
Pain					4 (5%) vs. 4 (4%)	4 (5%) vs. 3 (3%)	4 (5%) vs. 7 (8%)	4 (5%) vs. 8 (10%)		
Nervous system										
Headache					9 (10%) vs. 22 (25%)	9 (10%) vs. 17 (20%)	9 (10%) vs. 21 (24%)	9 (10%) vs. 16 (20%)	31 (11) vs. 43 (12)	31 (11) vs. 42 (11)

Any infection			34 (40%) vs. 47 (53%)	34 (40%) vs. 40 (47%)	34 (40%) vs. 56 (64%)	34 (40%) vs. 58 (73%)		
Serious Infection	2 (3.3) vs. 1 (1.8)	2 (3.3) vs. 5 (8.3)	5 (6%) vs. 1 (1%)	5 (6%) vs. 5 (6%)	5 (6%) vs. 5 (6%)	5 (6%) vs. 3 (4%)		
Upper respiratory tract infection			14 (16%) vs. 29 (33%)	14 (16%) vs. 17 (20%)	14 (16%) vs. 21 (24%)	14 (16%) vs. 18 (23%)	60 (21) vs. 94 (25)	60 (21) vs. 106 (28)
cough			3 (3%) vs. 8 (9%)	3 (3%) vs. 6 (7%)	3 (3%) vs. 11 (13%)	3 (3%) vs. 12 (15%)		
Nasopharyngitis / Rhinitis			4 (5%) vs. 5 (6%)	4 (5%) vs. 4 (5%)	4 (5%) vs. 6 (7%)	4 (5%) vs. 6 (8%)	17 (6) vs. 33 (9)	17 (6) vs. 40 (11)
Gastrointestinal disorders (total)								
vomiting								
Diarrhoea			10 (12%) vs. 7 (8%)	10 (12%) vs. 8 (9%)	10 (12%) vs. 7 (8%)	10 (12%) vs. 10 (13%)		
Abdominal pain			7 (8%) vs. 4 (4%)	7 (8%) vs. 8 (9%)	7 (8%) vs. 7 (8%)	7 (8%) vs. 6 (8%)		
Additional info available in study	Anti-ds DNA, Antibodies		Death,					

Comments:

a data estimated

bdata not shown or difficult to transfer

cComparison within patient or placebo group; no statistical comparision between patient and placebo group

Table 3b: Pharmacology data of clinical trials with infliximab in children and adults.

	CHILDREN (JIA) (4 to 17 years of age)		**ADULTS (RA)**			
Pharmacology	- Neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors (it does not neutralize TNFβ (lymphotoxin-α)).					
	- Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes.					
PD	- In RA, treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3].					
	- After treatment, patients exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes showed no significant decrease in number or in proliferative responses.					
Data Source	Ruperto 2007	Ruperto 2009	St.Clair 2004	Ternant 2013	Maini 1999	Mori 2006
Hematologic Events	A higher proportion of patients in the infliximab groups (1.7% and 8.8% in the 3 mg/kg and 6 mg/kg groups, respectively) as compared with placebo (0%) had at least 1 decrease in the absolute neutrophil count (<1.5x103 cells/μL and decrease ≥33%).			Systemic clearance increased with pre-infusion C-reactive protein concentration by 20%, varying from 3 to 14mg/l, and was decreased by 30% when MTX was co-administered.		

Immunology	Overall, 25% (26 of 102) of the patients with evaluable samples had antibodies to infliximab, with a higher incidence in the 3 mg/kg group (20 of 53 [38%]) compared with the 6 mg/kg group (6 of 49 [12%]). In addition, the antibody titers were notably higher among patients in the 3 mg/kg group, with 8 of 20 patients (40%) having a titer of 1:320 or higher (3 patients had titers of 1:20,480), compared with only 2 of 6 patients (33%) in the 6 mg/kg group. The safety profile for infliximab 3 mg/kg appeared to be less favourable in comparison with the 6-mg/kg dose.	During the OLE, 26/71 (37%) patients were positive for antibodies to infliximab,		ANAs	anti-dsDNA	Anti- infliximab	Antibodies toward infliximab were detected in the pre-infusion serum of three patients; two of these three patients were also treated with methotrexate and one was not. Of note, the infliximab concentrations for these three patients were below the limit of detection within 4 weeks after	Human antichimeric antibody (HACA) formation could not be measured in most patients receiving infliximab because serum infliximab interferes with the assay. However, of 27 infliximab-treated patients who stopped treatment before 30 weeks, 3 tested positive for HACA (2 with a titre of 1/10 and 1 with a titre of 1/40).	It is reported that HACA formation may possibly alter the pharmacokinetics of infliximab; however, HACA was not detected in patients with rapid clearance when their lowest serum concentrations of infliximab were below a detectable limit of assays.
			6mg/kg	34.3% patients	20.7% patients	6.7% patients	infliximab administration		
			placebo	11.3% patients	0.4% patients				
			One patient in the 6 mg/kg group developed a skin rash and ANA positivity, but tested negative for serum anti-dsDNA antibodies; this event was classified by the investigator as drug-induced lupus.						

PK								
Data Source		PI	Ruperto 2007	PI	St.Clair, 2004	Ternant 2013	Maini 1999	Mori 2006
		Phase III, international,		Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid	Multiple blood samples were obtained from each of 428 subjects with active RA who were enrolled in a multicenter, randomized, double-blind, placebo-controlled trial (ATTRACT). Pharmacokinetic modeling was used to predict the serum concentrations of infliximab after simulated infusions using doses and dosing intervals not evaluated in the trial.	Eighty-four patients treated with infliximab for RA were included in a prospective noncomparative study. They were analysed between two consecutive infliximab infusions.	International double-blind placebo-controlled phase III clinical trial, 428 patients who had active RA were randomized to placebo, 3mg/kg every 4 or 8 weeks or 10 mg/kg every 4 or 8 weeks. Patients were assessed every 4 weeks for 30 weeks.	Clinical pharmacokinetics (PK) of infliximab, using time–serum concentration profiles obtained from 21 RA patients who had received infliximab therapy in combination with methotrexate through 14 weeks. Patients receive an intravenous infusion of infliximab (3 mg/kg or 200mg) at weeks 0, 2, and 6,followed by maintenance therapy every 8 weeks.

			multicenter, randomized, double-blind, placebo-controlled study of infliximab therapy administered for 14 weeks, followed by a double-blind, all–active treatment extension through 44 weeks, in JRA patients receiving concomitant oral or parenteral MTX therapy.	Arthritis.		A total of 412 serum samples were available for analysis. Median (range) pre-infusion dose, dosing interval and infliximab concentrations were 3.6 mg/kg (2.5–6.8), 8.0 weeks (5.0–13.0) and 1.3 mg/l (<0.014–12.0), respectively.	Pharmacokinetic measurements were made in 197 patients.				
mean serum concentration [µg/mL]			3 mg/kg group had lower median serum concentrations of infliximab early in the study compared with the 6 mg/kg group.	At 8 weeks after a maintenance dose of 3 to 10 mg/kg, median infliximab serum concentrations ranged from approximately 0.5 to 6 µg/mL.			3mg/kg		10mh/kg		
							8 w.	1.5		8.9	
							4 w.	9.7		35.8	

	Population pharmacokinetic analysis showed that in children with JRA with a body weight of up to 35 kg receiving 6 mg/kg and children with JRA with body weight greater than 35 kg up to adult body weight receiving 3mg/kg, the steady state area under the concentration curve (AUCss) was similar to that observed in adults receiving 3 mg/kg.	The majority of patients receiving 3 mg/kg had detectable serum infliximab concentrations up to week 36, after which more patients in this group had lower-than-quantifiable trough levels of infliximab in their sera. At these later sampling time points, more than half of the patients receiving 3 mg/kg (i.e., 51.1% at week 44 and 52.4% at week 52) did not maintain quantifiable infliximab concentrations by the end of the 8-week interval separating infusions	However, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. Development of antibodies to infliximab increased infliximab clearance.				
Absorption				At week 0, 1 hour–postinfusion			
$C_{ss, trough}$ [µg/mL]							
C_{max} [µg/mL]				3 mg/kg	10 mg/kg		57(first intravenous 3mg/kg
				68.6	219.1		1h-postinfusion, n=5)
C_{min} [µg/mL]							Moderate EULAR(n=8) / Good EULAR(n=6)
							1.15±0.8 / 2.03±1.92
T_{max} [h]				1			1
average absolute bioavailability [%]							
partial AUC [µg·h/mL]							

Distribu-tion															
V_{ss} [L]														V / body weight: 0.05 L/kg (suggesting an intravascular pattern distribution)	
V_c [L]															
V_p [L]															
Elimina-tion															
Cl [mL/h]															
Q [mL/h]															
half-life [days]	3 mg/kg		6 mg/kg	7.7 to 9.5		Inflix-imab-MTX		Inflix-imab+ MTX		8–12 days, consistent with mainly an intravascular distribution.				0 to 2 w	2 to 6 w	6 to14w
	6.9		9.5			9.3		13						9.5 (n=8)	8.2 (n=5)	9.5 (n=9)
Additional Informa-tion															
Source: PI	No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender.														
	It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.														
	- Hematologic Events: Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE.														
	- Autoimmunity: Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome.														

Abbrevations:

PD: Pharmacodinamics

PK:Pharmacokinetics

$C_{ss, trough}$: steady-state trough concentration.

C_{max}: maximum serum concentration.

C_{min}: minimum serum concentration.

T_{max}: time to reach the maximum concentration.

V_{ss}: distribution volume.

V_c: Volume of distribution in the central compartment.

V_p: Volume of distribution in the peripheral compartment.

Cl: clearance.

Q: Intercompartment clearance.

EULAR: European League Against Rheumatism

w.: weeks

Table 4: Meta-Analysis: Results on ACR50 and ACR70 for etanercept showed a treatment effect for etanercept.

Type III Tests of Fixed Effects	**ACR 50**				**ACR 70**			
Effect	***Num DF***	***Den DF***	***F Value***	***P value***	***Num DF***	***Den DF***	***F Value***	***P value***
Treatment	5	7	12.23	0.0024	5	7	23.65	0.0003
Age group	1	7	0.19	0.6743	1	7	0.00	0.9688
Time in weeks	1	7	1.32	0.2878	1	7	0.02	0.8917

Table 5: Meta-analysis: Results on ACR50 and ACR70 for Adalimumab. Comparative data for adalimumab studies in children and adults confirmed a treatment effect in both groups.

Type III Tests of Fixed Effects	ACR 50				ACR 70			
Effect	***Num DF***	***Den DF***	***F Value***	***P value***	***Num DF***	***Den DF***	***F Value***	***P value***
Treatment	11	24	60.12	<.0001	11	24	33.60	<.0001
Age group	1	24	0.89	0.3542	1	24	3.01	0.0958
Time in weeks	1	24	1.51	0.2314	1	24	3.28	0.0825

However, there is no statistically significant treatment difference effect in the between-age or study-duration group for the endpoints ACR 50 and ACR 70.

Table 6: Meta-Analysis: Results on ACR50 and ACR70 for infliximab. Meta analysis of study data on infliximab shows no statistically significant treatment effect between adults and children.

Type III Tests of Fixed Effects	ACR 50				ACR 70			
Effect	***Num DF***	***Den DF***	***F Value***	***P value***	***Num DF***	***Den DF***	***F Value***	***P value***
Treatment	6	1	0.95	0.6559	6	1	1.56	0.5462
Age group	1	1	12.13	0.1780	1	1	8.07	0.2155
Time in weeks	1	1	3.08	0.3299	1	1	7.74	0.2197

We do not present forest plots for infliximab due to numerically instable results.

Etanercept

A single pediatric clinical trial (JIA-I [17]) in 2000 was identified from the drug prescribing information (Table 1a). This trial involved a total of 120 patients; 51 were part of a double-blind, placebo-controlled study with a nearly 1:1 ratio (26:25), and 69 participated in an open-label trial with etanercept only. A total of four studies in RA in adults, two in 1999 (Study I [18] and II [19]), one in 2000 (Study III [20, 21]) and one in 2004 (Study IV [22, 23]) were identified. Two compared etanercept with placebo, and two compared etanercept with methotrexate.

Dosage and Study Duration

Children were dosed for three to four months with 0.4 mg/kg bw etanercept, and a maximum of 25 mg per dose. Across all studies, adults received 10 or 25 mg etanercept over a period of six or twelve months. Only two trials [17, 24] included a placebo in the control arm and etanercept only in the study drug arm. All other trials in adults were performed in combination with methotrexate in experimental and placebo groups (Table 1a).

ACR Response

Assessment of the ACR study data differed between children and adults. The pediatric studies used the ACR30, ACR50 and ACR70 criteria and the adult studies the ACR20, ACR50 and ACR70 criteria. Thus, only the data for ACR50 and ACR70 could be considered for direct comparison (Table 1a and Figure 1). In addition, the selected time schedule for ACR assessment differed greatly between studies. While ACR50 and ACR70 were evaluated in week 12 or 16 in children, these were evaluated in week 4, 24 or week 48 in adults. Only Study II and Study IV showed an assessment in week 12. The respective numbers had to be estimated from figures in the publication. In the JIA study of Lovell et al., 64% of the 69 patients met the definition of 50% improvement, and 36% the definition of 70% improvement at the end of the study [17]. There was a similar rate in the Moreland et al., study (59% of the 25 mg group achieved an ACR20 response and 40% achieved an ACR50 response) at 24 weeks [24].

The response rate achieved with etanercept treatment in combination with methotrexate varied between 39-59% for ACR50 at 25 mg and 15-36% for ACR70 at 24 weeks in all other three studies in adults. Meta-analysis showed a treatment effect for etanercept in both, adults and children. However, no effect of age or study duration on the treatment effect could be measured (Table 4 and Figure 1). Thus, the results obtained on drug efficacy and dose showed no difference in adults and children.

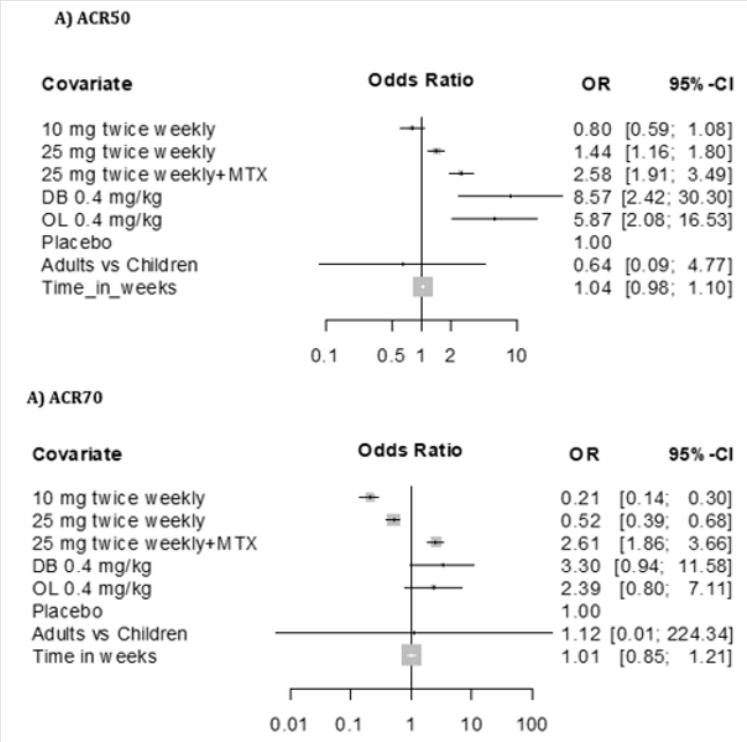

Figure 1: Forest plot results on ACR50 (A) and ACR70 (B) ETANERCEPT as graphical representation of the meta-analysis here includes five studies [17-20].

The first column shows names of the covariates in the model. Odds ratios for dose levels are reported with placebo as the reference. Results are shown together with 95% confidence interval. The black dot on each line shows you the odds ratio for each variable.

Meta-Analysis Results of ACR50 AND ACR70

Results of mixed-effects logistic regression for adults and children concerning treatment effects, age group (adults vs children) and study duration (time in weeks) can be viewed in the following tables. numDF, degrees of freedom of term; denDF, degrees of freedom of error term; F, variance ratio; P, error probability; critical value of significance: $p<0.05$.

Adverse Events

Most frequent adverse events (AEs) in both children and adults were injection site reaction, upper respiratory tract infection, headache, rhinitis, nausea and rash. The drug demonstrated a favorable risk-benefit profile in children and adults. No life-threatening events were observed (Table 1a).

Pharmacokinetics

The population pharmacokinetic analysis by Yim et al. confirmed that 0.8 mg/kg once weekly and 0.4 mg/kg twice-weekly subcutaneous regimens of etanercept had equivalent clinical outcomes. This served as a basis for the recent FDA approval of the 0.8 mg/kg once-weekly regimen in pediatric patients with JRA [25] (Table 1b).

Adalimumab

Two pediatric clinical trials, PJIA-I [26] and PJIA-II [27], were identified in the prescribing information. These were carried out in 2008 and 2014 and involved a total of 336 patients; 133 as part of a double-blind, placebo-controlled study (75 received methotrexate as supplemental therapy, 58 did not) and 203 in an open-label trial with adalimumab with or without methotrexate (112 and 91, respectively) (Table 2a). In comparison, five pivotal studies in adults, two in 2003 (RA-I [28] and RA-IV [29]), two in 2004 (RA-II [30] and RA-III [31]) and one in 2006 (RA-V [32]) were identified. Two compared adalimumab to placebo, and two were placebo-controlled plus methotrexate. One study compared adalimumab to methotrexate only, as well as to adalimumab plus methotrexate.

Dosage and Study Duration

The studies in children were carried out over 12 to 30 months with 24 mg/m^2 adalimumab, and a maximum of 20 or 40 mg per dose. Adults received 20, 40 or 80 mg over a period of six, six and a half or 13-24 months. The drug was given subcutaneously in all cases. The PI allows 10, 20 or 40 mg for children, depending on the body weight, and 40 mg is the approved dosage for adults as described in PI (Table 2a).

ACR response

Assessment of ACRs included were ACR30, ACR50, ACR70 and ACR90 for children, and ACR20, ACR50 and ACR70 for adults. Children were evaluated in week 12, 16, 24, 48, 60 and/or 96, and adults in week 24, 26, 52 and/or week 104. Thus, only ACR50 and ACR70 at 24 weeks are comparable (Table 2a and Figure 2). PJIA-II and RA-I, RA-III and RA-IV assessed ACR50 and ACR70 in week 24. However, these studies are not well comparable as their design differs considerably. PJIA-II was a placebo-controlled study, while RA-II and RA-III tested placebo plus methotrexate. RA-IV was also placebo-controlled, but allowed DMARDs during the study, whereas PJIA-II did not. Only studies with adalimumab in combination with methotrexate at week 24 were eligible for ACR50 and ACR70 comparative analyses. In the pediatric study PJIA-II, 83% of patients achieved ACR50, and in the adult RA-I study, 22% reached ACR50 at week 24 with 20 mg maximum dose treatment. In the PJIA-I study, ACR50 was achieved in 64% of the children at the 40 mg maximum dose compared with 37% in the RA-I study, 86% in the RA-III study and 59% in the RA-V study, respectively. 73% of children achieved ACR70 in the PJIA-II study, whereas only 7% and 9% of adult patients using 20 mg at 24 weeks were comparable as demonstrated in the RA-I and RA-II studies, respectively. At a 40 mg dose of adalimumab the response varied between 46% and 71% at weeks 16-48 in the PJIA-I study compared with 37%, 23%, 86% and 59% with the combination of adalimumab and methotrexate in adults in RA-I, RA-II, RA-III and RA-V studies, respectively.

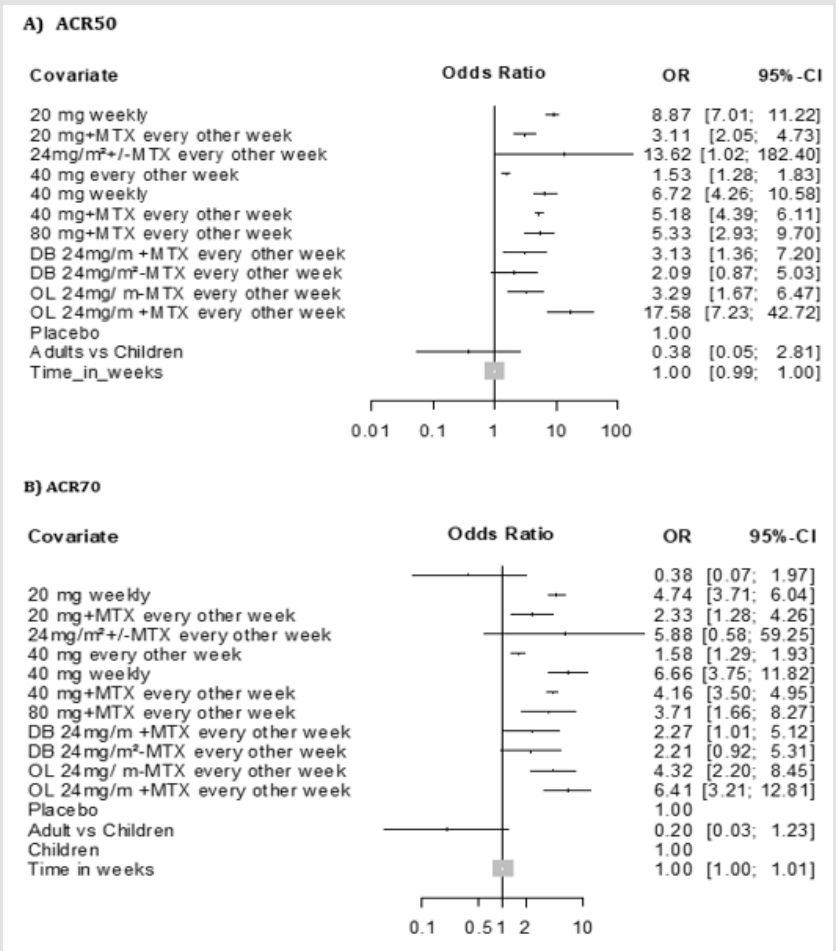

Figure 2: Forest plot results on ACR50 (A) and ACR70 (B) ADALIMUMAB, includes seven studies in the meta-analysis [25-31]. The first column shows names of the covariates in the model.

Odds ratios for dose levels are reported with placebo as the reference. Results are shown together with 95% confidence interval. Odds ratios for dose levels are reported with placebo as the reference. Results are shown together with 95% confidence interval.

Meta analysis of ACR50/70 revealed that comparative data for adalimumab studies in children and adults confirmed a treatment effect in both groups. However, there is no statistically significant treatment difference effect in the study duration for the endpoints ACR 50 and ACR 70 (Table 5 and Figure 2). Similar to etanercept, results obtained on adalimulab on efficacy and dose showed no difference in adult and children.

Adverse Events

The most common event was injection site reactions. The most common AEs leading to discontinuation of adalimumab treatment were clinical flare reaction, rash and pneumonia. The rate of serious infections was 4.6 per 100 patients (Table 2a).

Pharmacokinetics

A higher apparent clearance of adalimumab in the presence of Neutralizing anti-adalimumab antibody (AAA) and lower clearance with increasing age in patients aged 40 to >75 years was observed in population pharmacokinetic analyses in patients with RA. No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics. C_{max}, T_{max}, bioavailability and elimination values are only available for adults as described in the PI (Table 2b).

Golimumab

Golimumab has been confirmed to be an effective treatment for patients with RA in phase III clinical trials as evaluated by traditional measures of disease activity. The efficacy and safety profile of golimumab appears to be similar to other anti-TNF agents. However, golimumab has the potential advantage of once monthly subcutaneous administration and the possibility of both subcutaneous and intravenous administration. A study of CNTO 148 (golimumab) in children with juvenile idiopathic arthritis (GO-KIDS trial) to evaluate the efficacy and safety of golimumab is ongoing. This study enrolls patients who have active JIA and at least five joints with active arthritis that have poor response to methotrexate. The GO-KIDS trial consists of three parts and aims to assess the efficacy and safety of golimumab in pediatric patients aged 2 to <18 years with active JIA with a polyarticular course (at least five joints) despite therapy with methotrexate (10 to 30 mg/m^2/week) for at least 6 months [33]. The trial involved 173 patients (87.9% white, 75.7% female; median age 12 years, age 2 to 17 years) with moderately active disease. Nineteen (11%) patients discontinued in part 1 of the trial due to lack of efficacy (n=14), adverse effects (n=4), and withdrawal of consent (n=1).

Dosage and Study Duration

The drug (the usual adult dose for RA of an initial dose of 50 mg subcutaneously once a month or 2 mg per kg iv infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter. It should be given in combination with methotrexate. Corticosteroids, non-biologic DMARDs, analgesics and/or NSAIDs may be continued during treatment with this drug [33].

ACR Response

During the first phase of the trial, 151 of the remaining 173 (87.3%) patients achieved a 30% improvement from baseline in 3 of the 6 assessed criteria (active joint count, limitation of motion joint count, physician global assessment, patient/parent global assessment, Childhood Health Assessment Questionnaire, and acute-phase reactant level) without worsening of the remaining criteria, and 36.1% of patients displayed inactive disease status. The investigators randomized 154 patients to part 2 of the trial. The primary endpoint was not met; at week 48 the flare rates were comparable in those receiving placebo and golimumab (52.6% vs. 59.0%; P=0.41). The major secondary endpoints were also comparable between the placebo and treatment groups. The rates of inactive disease/clinical remission in patients receiving placebo + methotrexate or golimumab + methotrexate, for example, were 27.6%/11.8% and 39.7%/12.8%, respectively. Children with JIA in at least five joints displayed a rapid response to golimumab during the open-label, part 1 portion of the trial. During this portion of the trial, 36% of patients displayed inactive disease following the golimumab injection schedule. The sustained improvement in JIR was maintained in the placebo and treatment groups compared with baseline.

Adverse Events

Through week 48, adverse events, serious adverse events, and serious infections were reported in 87.9%, 13.3%, and 2.9% of all randomized patients, respectively. The most frequent serious adverse event was exacerbation of JIR. Death, active tuberculosis, or malignancy did not occur. Golimumab missed the primary endpoint in JIA. The reasons for the similarity in flare rates between the arms is unclear, and further study is needed if the regimen ultimately proves worthy of clinical use [33]. No Meta analysis for Golimumab on adult and pediatric data could be performed, as the data from the study in JIA is not publically available.

Infliximab

Study Description: A multicenter randomized double-blind placebo-controlled trial of infliximab in 117 children with polyarticular JIA did not find a statistically significant effect of infliximab 3 mg/kg intravenous infusion therapy plus methotrexate on ACR-Pedi responses as compared with placebo at 14 weeks [34]. The open-label extension (OLE, 52–204 weeks) of the study involved 78 patients. However, 34% discontinued infliximab prematurely, mostly by withdrawing consent due to lack of efficacy [35]. Overall, 30% of the children continued the study up to week 204 (Table 3a). The two pivotal studies in RA in adults were performed in 1999 (Study RA I, ATTRACT, [36]) and 2004 (Study RA II, ASPIRE, [37]). Both trials were placebo-controlled and allowed methotrexate. They worked with 3, 6 or 10 mg/kg i.v. application of infliximab.

ACR Response: After 14 weeks, following crossover from placebo to infliximab 6 mg/kg, ACR50 and ACR70 responses at week 52 were achieved in 70% and 52% of the children. However,

there was no statistically significant difference between the placebo group and the treatment group. Meta analysis supports that study data on infliximab shows no statistically significant treatment effect in children compared to adults. Also, the impact of age and study duration did not play a significant role (Table 6).

Adverse Events: The pediatric trial demonstrated that infliximab was safe, though the 3 mg/kg group had a less favorable safety profile, with a higher incidence of injection-site reactions and more serious infections. As the efficacy of infliximab in a pivotal study has not revealed a superior effect compared with placebo [34], the FDA did not approve infliximab for JIA, although it is still used in children. It is recommended as backup drug to treat JIA in the guidelines for JIA treatment [38] at the usual pediatric dose for JIA: 10 years or older: 3 mg/kg via iv infusion at weeks 0, 2, and 6, followed by infusions every 8 weeks [39]. Moreover, infliximab is approved for the therapy of refractory Crohn's disease in children over 6 years (Table 3a).

Pharmacokinetics: The childrens' trial observed formation of antibodies to infliximab, antinuclear antibody or anti-dsDNA antibodies in greater proportion in the 3 mg/kg group [34,35]. This confirmed results from one adult study [37], although other studies could not detect anti-chimeric antibodies, or only below detection limit [36,40,41] (Table 3b).

Discussion

The introduction of PIPs aimed to initiate a formal approval process for new medicinal products to avoid unauthorized use in children. In this review, the JIA indication in children, with RA as a counterpart in adults, and TNF-α blocking agents were selected as model diseases and drugs for comparison and evaluation of the data obtained from clinical studies in the new immunomodulatory drug space. TNF blocking agents are currently the only drug group with a number of compounds authorized in children and adults to treat JIA and in adults in RA, thus providing most experience in this drug class. Studies with etanercept in children showed the utility of TNF-α blocking agents in JIA for the first time. The PI for etanercept allows a dose of 0.8 mg/kg for children <63 kg and up to 50 mg for children ≥63 kg. 50 mg is also the approved dose for adults. The detailed PK parameters to support the dose selection in either population could not be identified and were addressed in only a few studies. A direct comparison of ACR response between children and adults was only partially possible as the time points for assessments differed considerably between both groups. Thus, it is unclear how the dose for children was selected. However, as the dose is set at a similar level for adults and children, these studies supported the idea that the dose for children could potentially have been extrapolated from the adult studies. Furthermore, no new safety issues or efficacy data were identified in proof-of-concept trials with children. Thus, the pediatric study results did not lead to any significant differences in dosage or safety profile compared with those in adults but confirmed the efficacy in JIA. Meta-analysis showed no difference on the treatment effect for etanercept in adults and children.

Similar findings were true for the comparison of dosage between adult and children for adalimumab. The PI shows a dose of 10, 20 or 40 mg for children, depending on the body weight; 40 mg is the approved dosage for adults. Thus, the pediatric study results did not lead to any significant differences in dosage that could not have been predicted from the adult studies. ACR response data was also only partially directly comparable due to difference in assessment values and schedules. In addition, no new safety and efficacy data was obtained by these studies. However, no statistically significant treatment difference effect in the beween-age or study-duration group for the endpoints ACR 50 and ACR 70 (Table 5) could be observed. Golimumab was used in trials described above in JIA or RA. So far, no new safety and efficacy aspects have been identified in the JIA study, but the primary endpoint was not met in children. Adverse effects with anti-TNF-α blockers are generally mild e.g. local skin reactions/infusion reactions, and are mostly transient. Minor infections e.g. upper respiratory tract infections are common. The risk of developing tuberculosis seems higher with the monoclonal antibody's infliximab and adalimumab, compared with etanercept [42,43]. Autoimmune phenomena such as drug-induced lupus, demyelinating disease, uveitis, psoriasis and inflammatory bowel disease were rather rare.

The risk of malignancies was reported to be increased in children. The post-marketing surveillance data on anti-TNF-α agents collected by the FDA reported 48 malignancies developing in children, of which 20 occurred in children with rheumatic conditions [44]. However, 88% of these children were also receiving other immunosuppressive drugs, including corticosteroids, azathioprine and methotrexate. Approximately 50% of the malignancies reported were lymphomas, leukemia and melanoma. The FDA and EMA added a boxed warning with regard to the possible increased risk of malignancy, especially lymphomas, in children treated with anti-TNF-α agents. Despite this, a recent summary of worldwide pediatric malignancies in children treated with etanercept did not find an overall increased risk. However, the authors acknowledged that it is difficult to assess the actual risk due to the rarity of malignant events, the underlying higher risk of lymphomas and leukemias in children with JIA and the confounding use of other immunosuppressants [45].

The time before the marketing approval of drugs is particularly important, as the overall aim of drug development in clinical trials should focus on patient benefit to make sure that access of drugs to patients is as simple and fast as possible. However, the studies performed to support marketing approvals in children does not seem to support this overall aim, as shown in the model based on

TNF-α blocking agents. Therefore, prolonging the drug approvals process does not benefit children, and promotes off-label pediatric used as these drugs are already marketed for use in adults. All four TNF-α blocking agents discussed here are approved in adults for RA, and all have been tested in children for JIA. The results broadly confirm the findings in adult studies other than infliximab, which has not been approved at a dose of 3 mg/kg for JIA (although it is continued to be used in children). Based on the similarity of dose administered in adults and children, the assumption is that the key parameters are likely to be similar across age groups for a range of biologics. Therefore, the question arises – is it important to carry out confirmatory studies in children? Are these studies really necessary or can the data for biologics be extrapolated if the expression of the respective target is the same in adults and children? The data reviewed suggests that the results obtained in adult RA studies are likely to be useful in predicting the dose, efficacy and safety for children with JIA. It therefore does not support further performance of extensive proof-of-concept studies in children.

Conclusions

The overall aim of drug development in clinical trials should focus on patient benefit, making sure that patient access to drugs is as simple and fast as possible. However, the studies performed to support marketing approvals in children do not seem to support this overall aim, and actually prolong the approvals process. They also promote off-label paediatric use as the drugs are already marketed for use in adults. All four of the TNF-α blocking agents discussed here are approved in adults for RA, and all have been tested in children in JIA. Based on the similarity of dose administered in adults and children for the two biologics approved in children, the assumption is that the key parameters are likely to be similar across age groups for a range of biologics. Therefore, the question arises – is it important to carry out confirmatory studies in children? Are large pivotal studies really necessary or can the data for biologics be extrapolated if the expression of the respective target is the same in adults and children? Our review of the data suggests that the results obtained in adult RA studies are likely to be useful in predicting the dose, efficacy and safety for children with JIA. It therefore does not support further performance of extensive proof-of-concept studies in children in specific targeted indications and based on mode of actions of a medicinal product.

However, infliximab and golimumab missed the primary endpoint for efficacy in JIA. The failure of these two drugs suggests that the differences in PK/PD parameters might play an important role in children's immune responses to biologic drugs, especially those expressed as chimeric or pegylated proteins. This differing immune response may have a bigger role in children than in adults, with higher levels of immunogenicity and neutralizing antibodies reducing the efficacy of the drugs. It is interesting to note that there were no studies identified in the public domain that looked at these drugs in terms of target expression in lymphocytes, or PK/PD studies in children. The data reviewed suggests that the results obtained in adult RA studies are likely to be useful in predicting the dose, efficacy and safety for children with JIA for certain products, however, the results from the two unapproved drugs might indicate that expression studies of the target and PK/PD studies are important to translate adult studies successfully in children. The need for further extensive efficacy and safety studies in children is therefore challenged. PK/PD studies plus modelling and simulation based on adult dose may be needed in children to help in finding optimal dose for children and to confirm a PD effect. In certain situations, for example in drugs of the same class, an extrapolation approach could avoid unnecessary further studies in the pediatric population.

Acknowledgment

We are very thankful to Dr. Richard Vesely (EMA, Rheumatology Division) for review of the manuscript and most valuable comments.

Declarations

a) None of the authors received any financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

b) Any of the authors consent to participate. Regarding the fact of a systematic review, ethics approval was not relevant.

c) All data which were discussed are given in the literature list.

d) None of the authors has competing interests

e) This article is a systematic review; therefore, no funding was necessary.

f) Authors' contributions: all authors interpretated and discussed the data and prepared the manuscript.

g) Acknowledgements are not to be listed.

References

1. GaBI (2015) Biosimilars of etanercept 2014 20 March.
2. GaBI (2014) Biosimilars of adalimumab. 20 February 2015.
3. EMA (2011) Assessment Report for Simponi (golimumab) Procedure No.
4. Pfizer (2015) Author's comment: Searching for 'Enbrel' at uprovides a download of the prescribing information and a link to additional information for health care professionals (this requires a login as a Pfizer employee or via DocCheck.

5. Abbott (2012) Author's comment: A search for Humira (adalimumab) on Abbot's website, brings up nine documents, including the 2012 Annual Report, the privacy policy and Abbott's Twitter feed, but no information about clinical trials.
6. https://www.novartis.com/
7. Roche (2015) Author's comment: Actemra (tocilizumab) leads to press releases that contain basic information about the drug and the pivotal studies.
8. https://www.actemra.com/
9. https://www.humira.com/
10. Ilaris. Author's comment: Ilaris (canakinumab) has its own website for downloading the full prescribing information. The site for health care professionals depicts important safety information for the medication but does not reveal information on clinical studies.
11. EMA. Author's comment: The European Medicines Agency (EMA) website allows searching for therapeutics and the respective European public assessment reports (EPAR). Every medicine granted a central marketing authorization by the European Commission is based on an assessment of the EMA's Committee for Medicinal Products for Human Use (CHMP). The page can be browsed for the medicine alphabetically, either under its trade name or under the generic name, for example Humira or adalimumab. The record includes approval status, indication, authorization details, product information and assessment history. EPAR summaries can be downloaded, and PIPs are also available.
12. European Union Clinical Trials Register. Author's comment: The European Union Clinical Trials Register lists all interventional clinical trials that are conducted inside the EU and the European Economic Area (EEA) as well as trials outside the EU/EEA that are linked to European paediatric drug development. At the day of access (4 February 2015) 24,783 clinical trials with a EudraCT protocol were registered, out of which 3375 were clinical trials conducted with subjects less than 18 years old. Another 10,296 older paediatric trials are stored that were conducted before the Paediatric Regulation in 2007 and in scope with the Art.45 of the Paediatric Regulation until 2006.
13. ClinicalTrials.gov. Author's comment: A registry and results database of publicly and privately supported clinical studies conducted worldwide. The website is based in the USA. It listed 183,742 studies with locations in all 50 US states and in 187 countries at the last access (7 February 2015). It is possible to search on the name of the drug. Advanced search includes the specific disease condition, titles, age group, study ID, and outcome measures, among others.
14. CenterWatch. Author's comment: CenterWatch is a US-based website and was the first to publish detailed information about active clinical trials that could be accessed by patients and their advocates. There is an option in 'Drug information' that allows searching for FDA-approved drugs. These can be viewed by year, company, conditions, therapeutic area or drug names. Drugs are listed by their trade names, not by their active substance, and include the company, the approval status and the treatment area. There is general information about the drug, a summary of the clinical results as to be found in the prescribing information, a list of the most common side effects, and a short explanation of the mechanism of action.
15. Google. Author's comment: The official clinical trial websites did not offer full access to key data on any of the clinical trials identified. The respective publications could be only be found by searching on www.google.com for the name of the drug, the disease condition, the study population or other information from the prescribing information.
16. Medline. Author's comment: The identified pivotal study was downloaded from Medline All pivotal studies were identified by and PubMed by name of the drug, disease condition, search term 'clinical trial' e.g. adalimumab, 'juvenile idiopathic arthritis' 'clinical trial'.
17. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, et al. (2000) Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 342(11): 763-769.
18. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, et al. (2000) Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther 22(1): 128-139.
19. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, et al. (1999) A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 340(4): 253-259.
20. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. (2000) A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 343(22): 1586-1593.
21. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, et al. (2002) Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 46(6): 1443-1450.
22. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, et al. (2004) Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 363(9410): 675-681.
23. Van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, et al. (2006) Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis 65(3): 328-334.
24. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, et al. (1999) Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 130(6): 478-486.
25. Yim DS, Zhou H, Buckwalter M, Nestorov I, Peck CC, et al. (2005) Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis. J Clin Pharmacol 45(3): 246-256.
26. Kingsbury DJ, Bader-Meunier B, Patel G, Arora V, Kalabic J, et al. (2014) Safety, effectiveness, and pharmacokinetics of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to 4 years. Clin Rheumatol 33(10): 1433-1441.
27. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, et al. (2008) Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 359(8): 810-820.
28. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, et al. (2003) Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 48(1): 35-45.
29. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, et al. (2003) Adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 30(12): 2563-2571.
30. Van de Putte L, Atkins C, Malaise M, Sany J, Russell AS, et al. (2004) Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 63(5): 508-516.
31. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, et al. (2004) Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody)

in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 50(5): 1400-1411.

32. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, et al. (2006) The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis & Rheumatism 54(1): 26-37.

33. Brunner HI, Ruperto N, Tzaribachev N, Horneff G, Wouters C, et al. (2014) A Multi-Center, Double-Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab in Pediatric Patients with Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy: Week 48 Results: Abstract 933. 2014 Annual Scientific Meeting of the American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP; 2014 16 November; Boston, 2014.

34. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, et al. (2007) A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 56(9): 3096-3106.

35. Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, et al. (2010) Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Ann Rheum Dis 69(4): 718-722.

36. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, et al. (1999) Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 354(9194): 1932-1939.

37. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, et al. (2004) Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 50(11): 3432-3443.

38. Oommen PT, Huppertz H-I (2013) Handlungsempfehlung nach der Leitlinie Therapie der Juvenilen idiopathischen Arthritis. Monatsschrift Kinderheilkunde 161(1): 60-62.

39. (2015) Drugs.com. Infliximab Dosage.

40. Mori S A (2007) relationship between pharmacokinetics (PK) and the efficacy of infliximab for patients with rheumatoid arthritis: characterization of infliximab-resistant cases and PK-based modified therapy. Mod Rheumatol 17(2): 83-91.

41. Ternant D, Ducourau E, Perdriger A, Corondan A, Le Goff B, et al. (2014) Relationship between inflammation and infliximab pharmacokinetics in rheumatoid arthritis. Br J Clin Pharmacol 78(1): 118-128.

42. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, et al. (2010) Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 69(3): 522-528.

43. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, et al. (2009) Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum 60(7): 1884-1894.

44. Diak P, Siegel J, La Grenade L, Choi L, Lemery S, et al. (2010) Tumor necrosis factor alpha blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration. Arthritis Rheum 62(8): 2517-2524.

45. McCroskery P, Wallace CA, Lovell DJ, Stryker S, Chernyukhin N, et al. (2010) Summary of worldwide pediatric malignancies reported after exposure to etanercept. Pediatr Rheumatol Online J 8: 18.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2021.39.006244

Jürgen Brunner. Biomed J Sci & Tech Res