Research Article

Biological Response Modifiers in Rheumatoid Arthritis: Metaanalysis of Efficacy

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ABSTRACT

Objectives: To analyze available evidence on the efficacy of different biological response. Modifiers which are used for a treatment of rheumatoid arthritis.

Methods: We searched systematically for randomized controlled clinical trials on treatment of rheumatoid arthritis with different biological response modifiers. Trials were searched from MEDLINE and Cochrane library database. Efficacy parameters ACR20, ACR50 ACR70 were analyzed for estimates combine Relative Risk (RR) and Number Need to Treat (NNT) using random effect model. Heterogeneity was evaluated by Cochrane's Q and I2 statistics.

Result: According to inclusion criteria, a total 42 trials (19,051) patients were included in this study. In general at ACR50 response etanercept (RR: 1.47, NNT: 1) is more efficacious as compared to other drugs. At recommended dose ACR20 response of adalimumab (RR: 2.42, NNT: 3) and at higher dose ACR 20 response of cetrolizumab (RR: 5.12, NNT: 2) most efficacious. At recommended dose level drugs is more efficacious if combine with methotrexate (ACR20 response, RR: 2.16, NNT: 3) as compared to methotrexate alone (RR: 1.38, NNT: 6) and placebo alone (RR: 2.61, NNT: 3).all the 42 trials provided evidence of significant heterogeneity with combine effect.

Conclusion: Among the biological response modifiers anti-TNF inhibitors are highly effective and more efficacious if combine with methotrexate for treatment of rheumatoid arthritis and among them priority given to etanercept.

Key words: Relative risk, Number needs to treat, Biological response modifiers, Meta-analysis, Rheumatoid arthritis

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INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic autoimmune disease characterized by inflammatory synovitis and progressive joint destruction which are associated with severe disability and increased mortality. There is currently no curative treatment for RA [1]. The goal of present day therapy in RA is to reduce the underlying joint inflammation and pain [1]. Major long term goals of therapy are to prevent joint destruction &deformity, maximize joint function and prevent co morbidities of disease and therapy including heart disease and osteoporosis. The management of RA rests on combination of non-pharmacological measures (physical, occupational, psychological, therapeutic approaches) and pharmacological measures like drug treatment (Disease Modifying Anti Rheumatoid Drugs (DMARDs), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids [2]. There are two classes of drugs in the management of RA: First line drugs (NSAIDs, Steroids) are used to inhibit local inflammatory symptoms but have no long lasting effects on the systemic aspects of RA and Second line drugs (DMARDs) are used to stop or even reverse the damage arising from chronic inflammation in cartilage or bone [3].

Now, several classes of biological response modifiers (biological) are available due to improved understanding of the pathogenesis of RA [4]. Biological are defined as "Pharmacological group of specific proteins with high molecular weight, specially targeting pro- inflammatory cytokines or cell surface antigens." Mechanism of action of biological contrasts to traditional DMARDs which target the overall inflammatory process of RA [2]. Method of action of biological is also more directed, defined and targeted. In comparison with DMARDs, biological has rapid clinical responses [5]. Patient experience improvements within a few weeks of starting treatment, Tumor Necrosis Factor (TNF) antagonists may provide benefit as early as few days after the first dose [6].

Biological are approved to treat moderate to severe RA that has not responded to conventional DMARDs. Overall, biological are highly effective in reducing RA symptoms, slowing disease progression and improving indices of physical function and quality of life. However, many questions about efficacy of this new class of drugs still remain unanswered: are all available biological equally effective, does their efficacy depend upon their being administered together with methotrexate (MTX), does efficacy depend on dose, are they more effective than MTX [6]. Till date, direct head to head evaluation of biological has not been reported in the literature. However results from clinical trials to date suggest that efficacy of this treatment is broadly comparable. An alternative approach to answering the efficacy related questions is to perform a systemic review with metaanalysis of relevant search. In this study, we conduct a metaanalysis of the efficacy of different biological at their different doses [7].

MATERIALS & METHODS

Study selection criteria

Randomized controlled clinical trials exploring the role of biological with any comparator for patients of RA were eligible for inclusion. For diagnosis and active disease of RA, patients had to satisfy the criteria of American College of Rheumatology (ACR).Trials with at least 6 months duration with efficacy measured by ACR response were included for the analysis [8]. Observational studies, clinical trial with other than recommended routes of administration, clinical trials with no treatment arm with recommended doses were not included in analysis. Only information published in the trial reports was assessed.

Efficacy parameters

We used ACR responses ACR20, ACR 50, ACR 70 (improvements of at least 20, 50 and 70% respectively on a series of predetermined measures) as efficacy parameters.

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Search Strategy

Clinical trials were searched in scientific journals. Information from the pubmed, Cochrane, clinical trial registry was checked using a high sensitivity strategy. The descriptors used were rheumatoid arthritis, biological response modifiers, Adalimumab, Cetrolizumab, Etanercept, Abatacept, Golimumab, Anakinra, Infliximab, Rituximab, Tocilizumab, randomized controlled trials, clinical trials and meat-analysis. The computerized search was completed with a manual search of reference lists from the published articles. There was English language restriction.

Data Extraction

Two investigators independently extracted the data from included trials using a standardized data extraction form. Trials with information only in abstract format were excluded. Data were extracted using key items for each trial: study design, patients' characteristics (sex, age and duration of disease evolution), patient inclusion criteria, drugs and doses used, treatment duration and ACR response.

Statistical analysis

For each single trial the Relative Risk (RR) of attaining an ACR response was obtained as a measure of the effect. Overall efficacy estimates (Combined relative risk) for each biological (as monotherapy or in association with MTX or another DMARD) compared to control (placebo, MTX or another DMARD) were attained using the ACR 20, ACR 50, and ACR 70 criteria as the main outcome variables. The number of patients needed for experimental treatment versus control (NNT) to obtain an additional positive ACR response was also estimated. We used random effect models for the analysis. Heterogeneity was evaluated using I2values & Cochrane's Q. Publication bias was assessed graphically using funnel plot. We used Microsoft excel sheet and the Medcalc software trial version 17.2 for analysis and presentation of main results [9].

RESULTS

Total 42 publications who met the selection criteria were included in the meta-analysis. We analyzed the entire set of 19,051 Patients recruited for the 42 trials selected: five using adalimuma (2585 patients), four using certolizumab (2064 patients), four using etanercept (1562 patients), three using abatacept (1148 patients), seven using golimumab (2859 patients), two using anakinra (660 patients), six using infliximab (2920 patients), three using rituximab (946 patients) and eight using tocilizumab (4307 patients). Table 1, shows the information of efficacy of drugs on ACR20, ACR50 and ACR70 responses.

Efficacy of drugs: Global analysis

We studies the efficacies of the biological response modifiers in the 42 trials included.(table-1) Global comparison of the ACR20 efficacy of any dose of any drug with any control treatment showed a combined effect of 1.99(95% CI 1.72-2.31) with NNT of 4(3-5). The combined effects were 2.19(1.21-3.98) for adalimumab trials, 1.04(2.34-7.00) for cetrolizumab, 1.36(0.93-1.97) for etanercept, 1.91(1.43-2.55) for abatacept, 1.77(1.34-2.34) for golimumab, 1.18(0.53-2.66) for ankinra, 1.68(1.23-2.30) for infliximab, 2.25(1.73-2.93) for rituximab and 2.13(1.67-2.71) for tocilizumab trials. Further analyses using ACR50 and ACR70 efficacies showed in Table 2 and Figure 1.

Effect refers to the risk of obtaining the corresponding response with drug relative to control treatment. 'Lower' and 'upper' represent the 95% confidence interval limits for the efficacy estimate. Random effect models.

Analysis of this set of 42 trials reduced the discriminating power of the funnel plot. It suggested a certain degree of asymmetry Figure 2, further analysis of subgroups based on previous exposure and response to DMARDs, mainly MTX, dose of drugs administered and control treatment selected (active or placebo, single or combined). The effects (RR) and NNT obtained with different doses of drugs were showed in Table 2 and Figures 3-5, the analysis of heterogeneity was showed in Table 3.

Analysis of the effect of different doses of drugs

We analyzed the efficacy of drug administration in three separate groups: currently recommended doses(adalimumab 40mg every 2 week, cetrilizumab 400mg at starting followed by 200mg every other week, etanercept 25mg twice a week, abatacept 10mg/kg / week, golimumab 50mg/4 week, ankinra 100mg/day infliximab 3mg/kg/8week, rituximab1000mg/2week, tocilizumab 4mg/kg/4 week), high doses(adalimumab 40mg/week, cetrolizumab 400mg at starting followed by 400mg every other week, golimumab100mg/4week, infliximab 3mg/kg/4 week, 6mg/kg/8week, 10mg/kg/8 week and 10mg/kg/4 week, tocilizumab 8 mg/kg/4week) and low doses(adalimumab 20mg/2week, etanercept 10 mg twice a week, abatacept 2mg/kg/week, ankinra 0.04mg/kg/day, 0.1mg/kg/day,0.4mg/kg/day and 1mg/kg/day, rituximab 500mg/2week, tocilizumab 2mg/kg/4 week). No patient treated with etanercept, abatacept, ankinra and rituximab received higher than recommended doses and no patient receiving cetrolizumab, golimumab and infliximab was prescribed lower than recommended doses. The combined and individual effects of drugs in subgroups based on the dose level were shown in Table-2.

NNT: number of patients needed to be treated

At recommended dose level, a stastically significant the combined and individual effects were seen in all drugs except for the etanercept and ACR70 response to tocilizumab. Accordingly , the NNTs for individual drugs and overall effect were positive except for the ACR70 response to cetrolizumab which has negative value and among them adalimumab,cetrolizumab and etanercept have low positive NNT value means more efficacious as compared to other drugs. Considering higher dose level, a stastically significant the combined and individual effects were seen in all drugs except for the adalimumab. Accordingly the NNTs for individual drugs and overall effect were positive except for the ACR20 and ACR50 response to adalimumab which has negative value and ACR70 response have high positive value and among them cetrolizumab is more efficacious having low positive NNT value. At low dose level, a stastically significant the combined and individual effects were seen in all drugs and accordingly NNTs were positive for all Table-2.

Table 1: Efficacy of biological response modifier drugs on ACR20, ACR50 and ACR70 responses.

Trials	Comparisons	Duration of trials	Groups	No. Of patients	ACR20 (3-6 month)	ACR50 (3-6 month)	ACR70 (3-6 month)	ACR20 (6-9 month)	ACR50 (6-9 month)	ACR70 (6-9 month)	ACR20 (9-12 month)	ACR50 (9-12 month)	ACR70 (9-12 month)	ACR20 (12-24 month)	ACR50 (12-24 month)	ACR70 (12-24 month)
								(6-9 month)								
Adalimumab																
Weinblatt et al. 2003 (n=271)	Adalimumab+methotrexate vs methtrexate+placebo	24wks	Adalimumab 20 mg/2 wk (s.c)+mtx	69				33	22	7						
			Adalimmab40mg/2 wk (s.c)+mtx	67				45	37	18						
			Adalimumab 80mg/2wk (s.c)+mtx	73				48	31	14						
			Placebo+mtx	62				9	5	3						
			Total adalimumab	209				126	90	39						
			Total	271												
Keystone et al. 2004 (n=619)	Adalimumab+methotrexate vs methtrexate+placebo	52wks	Adalimmab20mg/2wk(s.c)+mtx	212				129	87	37				116	80	44
			Adalimmab40mg/2wk(s.c)+mtx	207				131	81	43				122	86	48
			Placebo+mtx	200				59	19	5				48	19	9
			Total adalimumab	419				260	168	80				238	166	92
			Total	619												
Vandeput et al,2013(n=544)	Adalimumnab+placebo	26eks	Adalimumab20mg/wk(s.c)	106				38	20	9						
			Adalimumab40mg/wk(s.c)	112				44	23	11						
			Adalimumab20mg/every other wk(s.c)	113				52	25	14						
			Adalimumab40mg/every other wk(s.c)	103				55	36	19						
			Placebo	110				21	9	2						
			Total adalimumab	434				189	104	53						
			Total	544												
Breedveld et al,2006(n=799)	Methotrexate native	2yr	Adalimumab40mg/every otherwk(s.c)+mtx	268							196	166	123			
			Adalimumab40mg/wk(s.c)+placebo	274							148	112	71			
			Mtx+placebo	257							162	118	72			
			Total adalimumab	542							344	278	194			
			Total	799												
Miyasaka et al,2008(n=352)	Adalimumav vs placebo	24wk	Adalimumab20mg/every otherwk(s.c)	87	25	14	9									
			Adalimumab40mg/every otherwk(s.c)	91	40	22	11									
			Adalimumab80mg/every other wk(s.c)	87	44	28	13									
			Placebo every other wk	87	12	5	1									
			Total adalimumab	265	109	64	33									
			Total	352												
Cetrolizumab																
Keystone et al,2008(n=982)	Inadequate response to methotrexate	52wk	Cetrolizumab200mg+mtx	393	231	146	84									
			Cetrolizumab400mg+mtx	390	237	156	80									
			Placebo+mtx	199	27	15	6									
			Total cetrolizumab	783	468	302	164									
			Total	982												
Smolen et al,2008(n=619)	Inadequate response to methotrexate	24wk	Cetrolizumab200mg+mtx	246	141	80	39									
			Cetrolizumab400mg+mtx	246	142	81	26									
			Placebo+mtx	127	11	4	1									
			Total cetrolizumab	492	283	161	65									
			Total	619												
Feisclmann et al,2008(n=220)	Previous dmrds experienced	24wk	Cetrolizumab400mg+mtx	111	51	25	6									
			Placebo+mtx	109	10	4	0									
			Total	220												
Choy et al,2012(n=247)	Paritial response to mtx	24wk	Cetrolizumab400mg+mtx	124	57	22	0									
			Placebo+mtx	119	27	7	2									
			Total	243												
Etanercept																
Vander leijde et al,2006(n=682in originaltudy,n=522 complete 1 yr, n=421 complete 2 yr)	Previous dmrds other than mtx failed vs etanercept	2yr	Etanercept 25 mg twice weekly(s.c)+placebo/wk	223										167	120	60
			Mtx upto 20mg/wk orally+placebo twice weekly(s.c)	228										162	96	48

			Etancercept 25 mg twice weekly(s.c)+mtx/wk orally	231								199	164	113
			Etanercept 25 mg twice weekly(s.c)+placebo/wk	138								126	98	52
			Mtx upto 20mg/wk orally+placebo twice weekly(s.c)	119								101	68	37
			Etancercept 25 mg twice weekly(s.c)+mtx/wk orally	164								153	133	95
			Total etanercept	302								279	231	147
			Total	421										
Keystone et al, 2004(n=420)	Mtx experienced	16 wks	Etanercept 50 mg once weekly (n=214)	214	117	63	17							
			Etanercept 25 mg twice weekly (n=153)	153	96	50	12							
			Placebo for 8 weeks (n=53) followed by 25 mg etanercept twice weekly for 8 weeks	53	0	0	0							
			Totla etanercept	367	213	113	29							
			Total	420										
Bathon et al,(n=632)		12 month	Etanercept (10 mg) twice weekly subcutaneously (n=207) for 12 months	208					125	62	33			
			Etanercept 25mg twice weekly s.c	207					149	104	54			
			Methotrexate (19 mg) weekly orally (n=217) for 12 months	217					141	87	48			
			Total etanercept	415					274	166	87			
			Total	632										
Weinblattet et al,1999(n=89)	Etanercept vs mtx	24 wks	Etanercept 25 mg by twice weekly subcutaneous + methotrexate (n=59)	59	42	23	9							
			Placebo + methotrexate (n=30)	30	8	1	0							
			Total	89										
Abatacept														
Weinblatt et al, 2006(n=121)	Abatacept vs etanercept	1 yr	Abatacept (2 mg /kg) + etanercept(25 mg twice weekly) (n=85)	85	41	22	9		41	24	8			
			Placebo + etanercept (n=36)	36	11	7	0		11	6	2			
			Total	121										
Genove et al 2005,(n=389)	Abatacept vs placebo	24 wks	Abatacept 10 mg /kg intravenous infusion + dmards (n=258)	256	129	52	26							
			Placebo + dmards (n=133)	133	26	5	2							
			Total	389										
Kremer et al2006, (n=638)	Abatacept vs placebo	48 wks	Abatacept 10 mg/kg once monthly infusion+ methotrexate (n=433)	424	288	169	84		297	204	102			
			Placebo + methotrexate (n=219)	214	85	36	14		81	34	9			
			Total	638										
Golimumab														
Takeuchi et al,(n=308)	Dmards experienced placebo vs golimumab	24wks	Group 1 - every 4 week placebo (n=105)	105	20	6	1							
			Group 2 -golimumab 50 mg(n-101)	101	51	29	13							
			Group 3 - golimumab 100 mg (n=102)	102	60	33	12							
			Group 1 crossed over to 5o mg golimumab at week 16											
			Total golimumab	203	111	62	25							
			Total	308										
Smolen et al,2012(n=459)	Previous tnf-alpha inhibitors experienced placebo vs golimumab	160 wks	Group 1 - placebo	150					58	32	11			
			Group 2 - 50 mg golimumab	147					59	27	10			
			Group 3 - 100 mg golimumab	148					77	35	17			
			After 24 weeks, placebo group crossed over to 50 mg golimumab											
			Group 2 continued golimumab 50/100 mg per escape status											
			Group 3 maintained dosing											
			Total golimumab	295					136	62	27			
			Total	445										
Weinblatt et al,2013(n=592)	Mtx experienced antitnf naïve placebo vs golimumab	24wks	Placebo + methotrexate (n=197)	197	49	18	10							
			Golimumab (2 mg /kg) +methotrexate	395	231	118	55							
			Total	592										

Kay et al, 2008(n=172)	Mtx experienced	52wks	50 mg golimumab s.c.every 4 weeks + methotrexate(10 mg/week) (n=35)	35	21	13	3	25	18	8	
			50 mg golimumab s.c. every 2 weeks+ methotrexate(10 mg/week) (n=34)	34	17	8	5	20	10	7	
			100 mg golimumab s.c. every 4 weeks + methotrexate(10 mg /week) (n=34)	34	19	10	6	24	15	8	
			100 mg golimumab s.c.every 2 weeks+ methotrexate(10 mg/week) (n=34)	34	21	11	3	27	15	3	
			Placebo + methotrexate (n=35) (at 20 weeks,patients in placebo	35	13	2	0				
			Group began open label treatment with intravenous infusion of infliximab at 3 mg/kg								
			Combined	137	84	42	17				
			Total golimumab	137	78	42	17				
			Total	172							
Keystone et al,2008(n=444)	Mtx experienced		Group 1 - placebo injections + methotrexate capsules (n=133)	133	44	13	5				
			Group 2 - golimumab 100 mg injections + placebo capsules (n=133)	133	59	27	10				
			Group 3 - golimumab 50 mg injections + methotrexate capsules (n=89)	89	49	31	12				
			Group 4 - golimumab 100 mg injections + methotrexate capsules (n=89)	89	50	26	8				
			Injections were administered subcutaneously every 4 weeks								
			Total golimumab	311	158	84	30				
			Total	444							
Emery et al 2009(n=634)	Mtx experienced	24 wks	Group 1 - placebo + methotrexate (n=160)	160	80	48	24				
			Group 2 - golimumab 100 mg + placebo (n=159)	159	87	51	22				
			Group 3 - golimumab 50 mg + mehotrexate (n= 159)	159	103	67	40				
			Group 4 - golimumab 100 mg + methotrexate (n=159)	159	103	54	32				
			Total golimumab	477	293	172	94				
			Total	637							
Tanaka et al 2011(n=261)	Mtx experienced	24 wks	Group 1 - placebo + methotrexate (n=88)	88	24	8	2				
			Group 2 - golimumab 50 mg + methotrexate (n=86)	86	62	37	19				
			Group 3 - golimumab 100 mg + methotrexate (n= 87)	87	65	33	12				
			Total golimumab	173	127	70	31				
			Total	261							
Anakinra											
Cohen et al,2002(n=419)	Mtx+placebo vs mtx+anakinra	24wk	Anakinra 0.04mg/kg/day, s.c+mtx	63	16	3	1				
			Anakinra 0.1mg/kg/day, s.c+mtx	74	26	11	2				
			Anakinra 0.4mg/kg/day, s.c+mtx	77	19	4	2				
			Anakinra 1mg/kg/day, s.c+mtx	59	27	11	3				
			Anakinra 2mg/kg/day, s.c+mtx	72	27	17	8				
			Placebo	74	14	3	0				
			Total ankinra	345	115	46	16				
			Total	419							
Genovece et al	Pt already received mtx, etanercept+placebo vs etanercept+ankinra	24 wk	Etanercept+placebo	80	54	33	17				
			Etanercept 25mg twice /wk ,s.c+ankinra100mg/day, s.c	81	50	25	11				
			Etanercept 25mg once /wk ,s.c+ankinra100mg/day, s.c	80	41	31	19				
			Total ankinra	161	91	56	30				
			Total	241							
Infliximab											
Chunzhanget al	Mtx+placebo vs mtx+infliximab	18wk	Mtx+placebo	71	35	18	10				
			Mtx+infliximab 3mg/kg	78	59	34	28				
			Total	149							

Clair et al	Mtx+placebo vs mtx+infliximab	54 wk	Mtx+placebo	274								147	88	58
			Mtx+infliximab 3mg/kg	351								219	161	114
			Mtx+infliximab 6mg/kg	355								235	179	132
			Total infliximab	706								454	340	246
			Total	980										
Lipsky et al	Mtx+placebo vs mtx+infliximab	54 wk	Mtx+placebo	88								15	7	2
			Mtx+infliximab 3mg/kg every 8wk	86								36	18	9
			Mtx+infliximab 3mg/kg every 4wk	88								42	30	15
			Mtx+infliximab 10mg/kg every 8wk	87								51	34	22
			Mtx+infliximab 10mg/kg every 4wk	81								48	31	15
			Total infliximab	342								177	113	61
			Total	430										
Quinn et al	Mtx+placebo vs mtx+infliximab	54wk	Mtx+placebo	10								6	4	3
			Mtx+infliximab	10								8	8	7
			Total	20										
Sciffet al	Mtx+placebo vs mtx+infliximab	26wk	Mtx+placebo	107				45	21	10				
			Mtx+infliximab(3mg/kg)	152				90	56	37				
			Total	259										
Westhovens et al	Mtx+placebo vs mtx+infliximab	22wk	Mtx+placebo	361	87	33	16							
			Mtx+infliximab 3mg/kg	360	199	110	48							
			Mtx+infliximab 10mg/kg	361	205	119	54							
			Total infliximab	721	404	229	102							
			Total	1082										
Rituximab														
Cohen et al	Mtx+placebo vs mtx+rituximab	24wk	Mtx+placebo	201	36	10	2							
			Mtx+rituximab(2*1000mg)	298	152	80	36							
			Total	499										
Edward et al	Mtx+placebo vs mtx+rituximab	24wk	Mtx+placebo	40	15	5	2							
			Mtx+rituximab(2*1000mg)	40	29	17	9							
			Total	80										
Emery et al	Placebo vs rituximab	24 wk	Placebo	122	34	16	6							
			Rituximab(2*500mg) iv infusion	123	68	41	16							
			Rituximab(2*1000mg) iv infusion	122	66	41	24							
			Total rituximab	245	134	82	40							
			Total	367										
Tocilizumab														
Emery et al	Mtx+placebo vs mtx+tcz	24wk	Mtx+placebo	127	13	5	2							
			Mtx+tcz 4mg/kg	138	42	23	7							
			Mtx+tcz8mg/kg	152	76	44	19							
			Total tcz	290	118	67	26							
			Total	417										
Genovere et al	Dmards+placebo vs dmards+tcz	24wk	Dmards+placebo	370	93	33	11							
			Dmards+tcz(8mg/kg every 4 wk)	751	458	285	158							
			Total	1121										
Jones et al	Mtx+placebo vs mtx+tcz	24wk	Mtx+placebo	262	138	88	40							
			Mtx+tcz(8mg/kg every 4 wk)	268	187	118	75							
			Total	530										
Kremer et al	Mtx+placebo vs mtx+tcz	52wk	Mtx+placebo	393								98	39	20
			Mtx+tcz 4mg/kg	399								200	120	48
			Mtx+tcz 8mg/kg	398								219	139	60
			Totla tcz	797								419	259	108
			Total	1190										
Mani et al	Mtx+placebp vs mtx+tcz	16wk	Mtx+placebo	40	16	12	6							
			Mtx+tcz 2mg/kg	46	29	15	6							
			Mtx+tcz 4mg/kg	42	26	16	5							
			Mtx+tcz 8mg/kg	43	32	23	16							
			Total tcz	131	87	54	27							
			Total	171										
Nishimoto et al samuri	Dmards vs tcz	52wk	Dmards	131								45	17	8
			Tcz 8mg/kg	134								105	86	59
			Total	265										
Nishimoto et al satori	Mtx+placebo vs mtx+tcz	24wk	Mtx+placebo	33	8	6	3							
			Mtx+tcz 8mg/kg	54	43	27	16							
			Total	87										
Yazici et al	Dmards+placebo	24wk	Dmards+placebo	173	43	19	5							
	Dmards+tcz		Dmards+tcz(8mg/kg)	353	159	106	53							
			Total	526										

Table 2: Effects (RR and NNT (95% CI)) obtained with different doses of biological response modifier drugs.

		All doses of drugs vs. control		Recommended doses of drugs vs. control		Higher doses of drugs vs. control		Lower doses of drugs vs. control	
Biological response modifiers	ACR	RR (CI95%)	NNT (CI 95%)	RR (CI95%)	NNT (CI 95%)	RR (CI95%)	NNT (CI 95%)	RR (CI95%)	NNT (CI 95%)
Adalimumab	ACR20	2.19(1.21-3.98)	4(2-9)	2.42(1.40-4.20)	3(2-6)	2.27(0.88-5.81)	4(-31-2)	2.21(1.83-2.68)	4(3-5)
	ACR50	3.05(1.26-7.39)	5(3-9)	3.54(1.57-8.00)	4(3-6)	2.71(0.89-8.25)	6(-114-3)	3.67(2.63-5.12)	5(3-11)
	ACR70	4.38(1.37-14.00)	8(7-11)	5.39(1.81-16.08)	6(5-8)	3.35(0.87-12.96)	12(6-483)	5.37(2.85-10.12)	9(7-14)
Cetrolizumab	ACR20	1.04(2.34-7.00)	3(2-3)	4.02(2.34-6.89)	3(2-3)	5.12(3.54-7.41)	2(2-2)		
	ACR50	5.27(3.38-8.22)	4(3-7)	5.17(3.33-8.03)	4(3-7)	6.52(3.51-12.12)	3(3-4)	No trial	
	ACR70	5.55(1.34-23.08)	12(-34-5)	5.78(1.32-25.28)	11(-24-4)	7.50(3.54-15.90)	7(5-18)		
Etanercept	ACR20	1.36(0.93-1.97)	4(-8-1)	1.46(0.95-2.23)	3(2-13)			Single trial	
	ACR50	1.47(0.89-2.44)	1(0-1)	1.57(1.00-2.48)	4(3-11)	No trial			
	ACR70	1.42(0.81-2.46)	11(6-49)	1.47(1.00-2.17)	10(6-22)				
Abatacept	ACR20	1.91(1.43-2.55)	4(3-4)	2.17(1.27-3.70)	3(3-4)				
	ACR50	2.46(1.32-4.58)	6(4-10)	3.22(1.45-7.13)	5(4-8)	No trial		Single trial	
	ACR70	3.45(2.09-5.67)	9(7-13)	3.44(1.93-6.13)	9(6-17)				
Golimumab	ACR20	1.77(1.34-2.34)	4(3-7)	1.77(1.33-2.35)	4(3-7)	1.76(1.26-2.47)	4(3-9)		
	ACR50	2.55(1.48-4.41)	6(4-10)	2.72(1.56-4.74)	5(3-9)	2.17(1.19-3.97)	7(4-23)	No trial	
	ACR70	2.50(1.41-4.42)	12(8-19)	2.98(1.87-4.76)	9(7-12)	2.15(1.10-4.19)	16(10-38)		
Ankinra	ACR20	1.18(0.53-2.66)	50(-4-4)						
	ACR50	1.51(0.36-6.26)	48(-6-5)	Single trial		No trial		Single trial	
	ACR70	1.67(0.22-12.77)	74(16-5)						
Infliximab	ACR20	1.68(1.23-2.30)	4(3-7)	1.61(1.21-2.15)	5(3-8)	2.05(1.13-3.72)	4(2-8)	No trial	
	ACR50	2.21(1.51-3.23)	5(4-6)	2.02(1.45-2.85)	6(5-7)	2.85(1.36-5.95)	4(3-6)		
	ACR70	2.49(1.72-3.61)	7(6-10)	2.26(1.63-3.14)	9(6-13)	3.01(1.42-6.37)	7(5-11)		
Rituximab	ACR20	2.25(1.73-2.93)	3(3-4)	2.24(1.71-2.95)	3(3-4)			Single trial	
	ACR50	3.51(2.15-5.72)	5(4-6)	3.54(2.16-5.79)	5(4-6)	No trial			
	ACR70	4.87(2.27-10.44)	9(7-12)	5.21(2.70-10.09)	8(6-12)				
Tocilizumab	ACR20	2.13(1.67-2.71)	3(3-4)	2.02(1.54-2.64)	4(3-5)	2.22(1.71-2.87)	3(2-4)		
	ACR50	2.87(1.82-4.51)	5(4-6)	2.45(1.27-4.73)	6(4-10)	3.05(1.92-4.83)	4(3-5)	Single trial	
	ACR70	3.53(2.15-5.79)	9(8-11)	1.84(0.88-3.85)	21(12-74)	3.93(2.43-6.35)	6(5-9)		
Overall	ACR20	1.99(1.72-2.31)	4(3-5)	2.00(1.70-2.35)	4(3-4)	2.24(1.81-2.78)	3(3-4)	1.81(1.29-2.56)	5(3-9)
	ACR50	2.68(2.19-3.29)	5(4-6)	2.69(2.18-3.32)	5(4-6)	2.92(2.15-3.96)	5(4-6)	2.08(1.18-3.67)	8(5-32)
	ACR70	3.03(2.38-3.85)	9(8-11)	2.85(2.25-3.65)	9(7-12)	3.38(2.38-4.80)	8(7-11)	2.80(1.21-6.47)	15(9-44)

RR (CI 95%): relative risk (95% confidence limits); NNT: number of patients needed to be treated

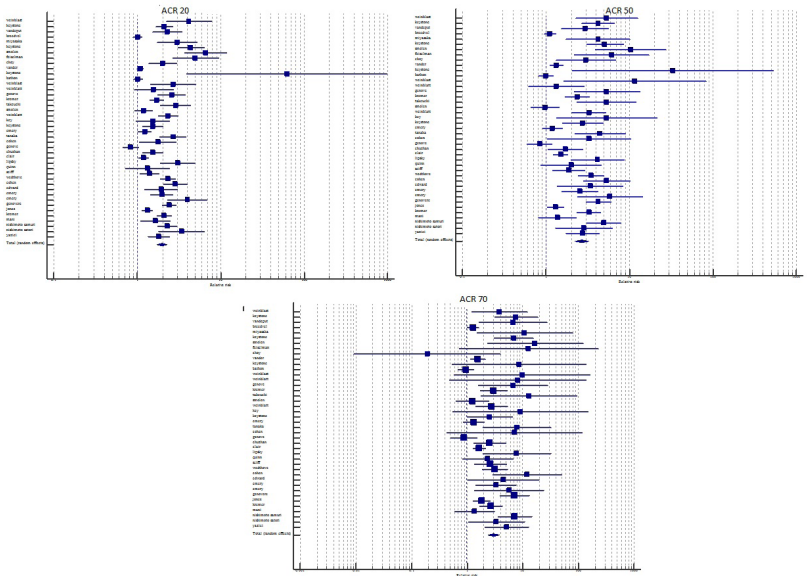

Figure 1: Efficacy of all doses of anti-TNFα drugs on ACR20, ACR50 and ACR70 responses. Effect refers to the risk of obtaining the corresponding response with drug relative to control treatment. 'lower' and 'upper' represent the 95% confidence interval limits for the efficacy estimate. Random effect models.

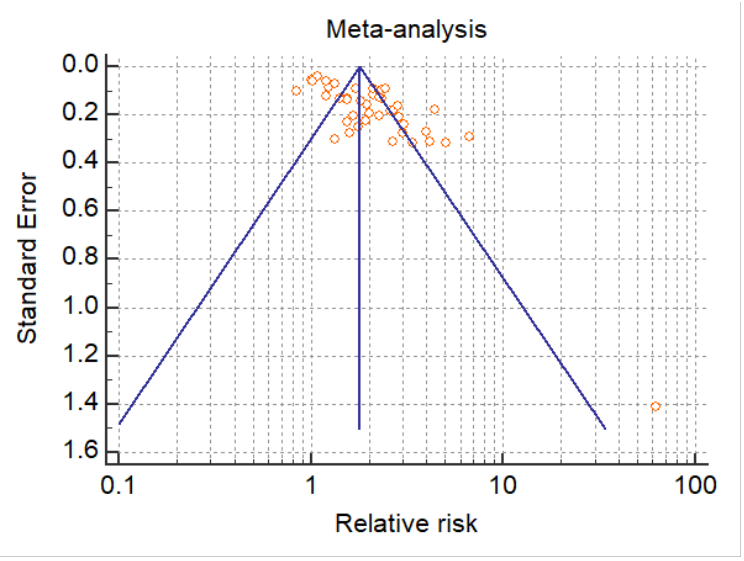

Figure 2: Funnel plot of selected studies. The x-axis shows effect estimates (RR) on alogarithmic scale while y-axis measures the precision of each study.

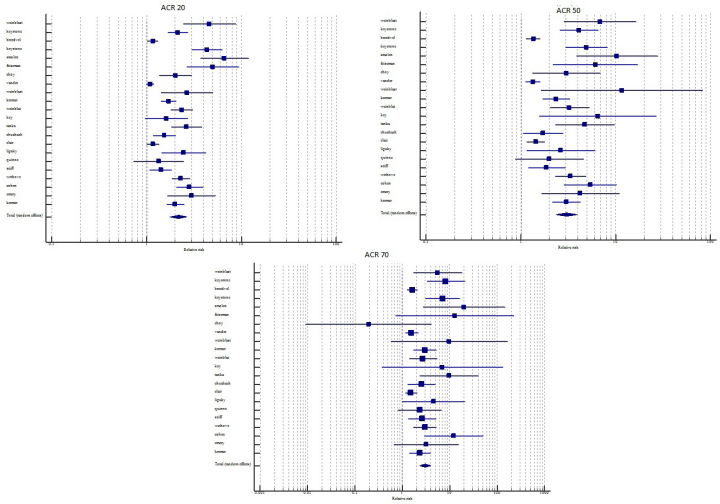

Figure 3: Efficacy of anti-TNFα drugs at standard doses in combination with Methotrexate compared with methotrexate in combination with placebo. Effect refers to the risk of obtaining the corresponding response with drug relative to control treatment. 'Lower' and 'Upper' represent the 95% confidence interval limits for the efficacy estimate. Random effect models.

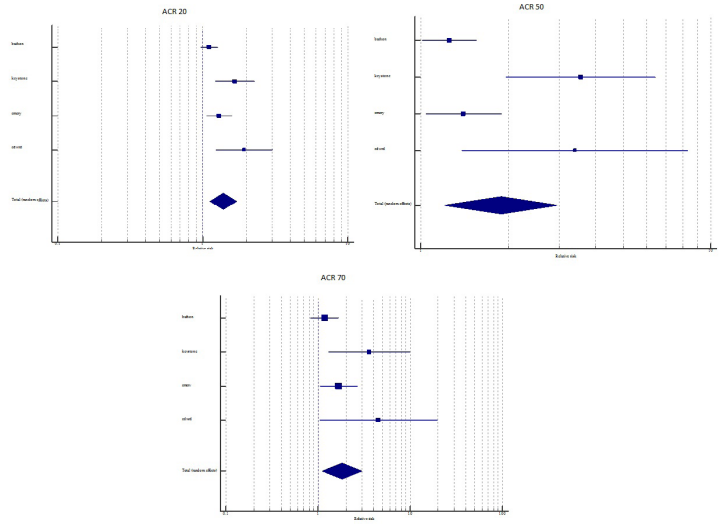

Figure 4: Efficacy of anti-TNFα drugs at standard doses compared with methotrexate alone. Effect refers to the risk of obtaining the corresponding response with drug relative to control treatment. 'Lower' and 'Upper' represent the 95% confidence interval limits for the efficacy estimate. Random effect models.

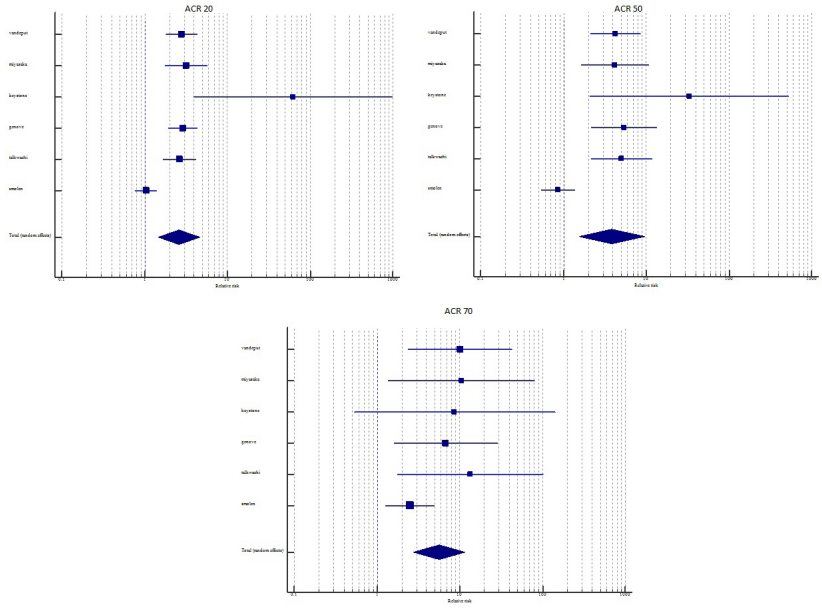

Figure 5: Efficacy of anti-TNFα drugs at standard doses compared with placebo alone Effect refers to the risk of obtaining the corresponding response with drug relative to control treatment. 'Lower' and 'Upper' represent the 95% confidence interval limits for the efficacy estimate. Random effect model.b

Table 3: Efficacy and heterogeneity of drugs at various doses and different groups.

Comparisons(drugs vs control)	ACR response	Drug Events/Total	Control Events/ Total	RR (CI 95%)	NNT (CI 95%)	Q	I2 %(CI 95%)	p-value
All doses of drugs vs. control	ACR20	7576/13154	1940/5898	1.99(1.72-2.31)	4(3-5)	622	93.41(91.93-94.62)	p<0.0001*
	ACR50	4663/13154	974/5898	2.68(2.19-3.29)	5(4-6)	400	89.76(85.10-91.88)	p<0.0001*
	ACR70	2438/13154	467/5898	3.03(2.38-3.85)	9(8-11)	187	78.08(70.78-83.56)	p<0.0001*
Recommended doses of drugs vs. control	ACR20	3840/6474	1585/4818	2.00(1.70-2.35)	4(3-4)	484	92.97(91.18-94.40)	p<0.0001*
	ACR50	2369/6474	801/4818	2.69(2.18-3.32)	5(4-6)	260	86.90(82.79-90.03)	p<0.0001*
	ACR70	1263/6474	400/4818	2.85(2.25-3.65)	9(7-12)	114	70.18(57.98-78.84)	p<0.0001*
Higher doses of drugs vs. control	ACR20	3024/5184	1171/3730	2.24(1.81-2.78)	3(3-4)	315	93.34(91.16-94.99)	p<0.0001*
	ACR50	1911/5184	610/3730	2.92(2.15-3.96)	5(4-6)	252	91.66(88.71-93.85)	p<0.0001*
	ACR70	1022/5184	299/3730	3.38(2.38-4.80)	8(7-11)	122	82.75(74.92-88.14)	p<0.0001*
Lower doses of drugs vs. control	ACR20	590/1216	317/948	1.81(1.29-2.56)	5(3-9)	66	87.81(79.00-92.92)	p<0.0001*
	ACR50	317/1216	163/948	2.08(1.18-3.67)	8(5-32)	65	87.69(78.76-92.87)	p<0.0001*
	ACR70	139/1216	71/948	2.80(1.21-6.47)	15(9-44)	38	79.19(60.99-88.90)	p<0.0001*
Drug at recommended dose plus methotrexate vs. placebo plus methotrexate	ACR20	2780/4589	1067/3388	2.16(1.75-2.68)	3(3-4)	365	94.24(92.45-95.61)	p<0.0001*
	ACR50	1758/4589	530/3388	3.03(2.33-3.94)	4(4-5)	171	87.73(82.77-91.27)	p<0.0001*
	ACR70	964/4589	275/3388	3.06(2.31-4.05)	8(6-12)	68	69.25(52.38-80.15)	p<0.0001*
Drug at recommended dose vs. methotrexate	ACR20	330/495	280/550	1.38(1.10-1.73)	6(4-14)	11	72.78(23.19-90.35)	P=0.0116*
	ACR50	219/495	153/550	1.89(1.21-2.95)	6(4-11)	15	79.67(46.02-92.35)	P=0.0020*
	ACR70	115/495	79/550	1.81(1.10-2.99)	11(8-23)	7.3	58.82(0.00-86.29)	P=0.0633
Drug at recommended dose vs. placebo	ACR20	547/1065	134/638	2.61(1.46-4.67)	3(2-10)	44	88.60(77.76-94.16)	p<0.0001*
	ACR50	279/1065	57/638	3.84-1.53-9.64)	5(3-12)	37	86.30(72.35-93.22)	p<0.0001*
	ACR70	125/1065	17/638	5.65(2.76-11.58)	10(8-14)	7.1	29.96(0.00-71.43)	P=0.2105

RR (CI 95%): relative risk (95% confidence limits); NNT: number of patients needed to be treated; Q: cochrane's Q; I2%: percentage of variability in study results attributable to between-study differences; *statistical significant

Analysis of the effect of drugs at recommended dose base on previous exposure and response to DMARDs and control treatment selected

Twenty two trials compared the effects of drugs plus MTX with placebo plus MTX. A stastically significant beneficial combined effect is seen in the ACR20 response with an RR of 2.16(1.75-2.68) and an NNT of 3(3-4). Analyses using the ACR50 and ACR70 response showed significant result Table-2 and Figure-3. Four trials assessed the effects of drugs with MTX alone, showing a stastically significant combined positive effect on the ACR20 response with an RR of 1.38(1.10-1.73) and an NNT of 6(4-14).ACR50 and ACR70 also showed significant results Table-3 and Figure-4. Six trials compare the effects of drugs with placebo alone, showing a stastically significant combined positive effect on the ACR20 response with an RR of 2.61(1.46-4.67) and an NNT of 3(2-10).ACR50 and ACR70 also showed significant results Table-3 and Figure-5.

Analysis of heterogeneity at various dose levels and in different subgroups

All the 42 trials provided evidence of stastically significant heterogeneity with combined effects of ACR20(Q=622.43;I% 93.45%;p<0.0001), ACR50(Q=400.49;I% 89.76%;p<0.0001 and ACR70 responses(Q=187.05;I% 78.08%;p<0.0001). At recommended, higher and lower dose level drug trials suggested stastically significant heterogeneity with combined effects of all responses. Among the different subgroups at recommended dose level provided stastically significant heterogeneity with combined effects of all responses except trials compare the combined effects of ACR70 response of drugs with placebo alone and drugs with MTX alone subgroup Table-3.

DISCUSSION

During the last decade, concept of Evidence Based Medicine (EBM) caused great interest among health professionals. According to definition Evidence Based Medicine represents integration of clinical expertise, patient's values and best available evidence in process of decision making related to patients health care. Medical knowledge grows every day, so that previously accepted facts rapidly become old and it seems impossible to follow such explosion of scientific information. There are clear difficulties when clinician needs to keep step with the new achievements published in medical journals [10].

The task of staying current, although never easy, is made much simpler by incorporating the tools of EBM such as the ability to track down and critically appraise evidence, and incorporate it into everyday clinical practice [11].

In rheumatology clinical practice, one of the major decisions with which rheumatologists are confronted is the choice of treatment for their patients. Although there is increasing appreciation of evidence based medicine, the data sources for this are still in their infancy. Guidelines and algorithms have been developed to help determine the appropriate choices of treatment, but they are not applicable to every patient. Moreover, new information from clinical trials is being published at too fast a rate for textbooks to remain current. The challenge is to translate the clinical research data into a format suitable for use by busy clinicians in practice. One key item of information needed for an informed decision is an easily understood estimate of the magnitude of benefit (and risk of adverse effects) that can be used by doctors and other care givers. Those most commonly used in rheumatology include event rates, relative risk, relative risk reduction, absolute risk reduction or risk difference, and odds ratios. In addition, a number of rheumatological measures are based on continuous outcomes—for example, number of tender joints or swollen joints. Many of these are difficult for the clinicians to use in clinical practice for reasons that include their complexity, the difficulty in assessing the clinical importance of a specific result, and the challenge in comparing benefits with risks/adverse effects. One approach that is becoming increasingly used in other disciplines is the "number needed to treat" (NNT). The advantage of the NNT over the relative risk and RRR is that it expresses both the risk without treatment and the risk reduction with treatment. In addition, the NNT informs the clinicians and patients how much effort they must spend to prevent one event and allows comparison of the amount of effort needed to prevent the same event with other treatment options [12].

Produced in living systems, biologics comprise a group of recombinant proteins including antibodies and cytokine inhibitors. Following their introduction a seismic shift has occurred in the management of RA and a therapeutic landscape without them now seems inconceivable. The ascent of biologics occurred as a consequence of greater understanding of the proinflammatory mediators involved in the disease. At the vanguard have been tumor necrosis factors alpha antagonism and interleukin-1 and 6 antagonists. In contrast to cytokine blockade which targets downstream mediators of joint inflammation, anti–cellular biologics target cells that are proposed to coordinate the immunopathology of RA [13]. Currently available agents target two key players in RA pathogenesis: B cells and T cells. B cells are targeted and killed by rituximab, whereas T cells are modulated by abatacept, which interferes with their activation without killing them [14].

Considering NNT in general etanercept is more efficacious followed by cetrolizumab, rituximab and tocilizumab. At recommended doses adalimumab, cetrolizumab, etanercept, abatacept and rituximab are equally efficacious. At higher doses cetrolizumab is more effective. Overall drugs are more efficacious at higher and recommended dose level as compared to lower dose level. Review done by Curtis JR and Singh JA showed significantly greater proportions of patients treated with infliximab, etanercept or adalimimab achieved ACR20, ACR50 and ACR70 response than control patients. A systematic review of the efficacy of TNF antagonist calculated a NNT of 5-6 for at least an acceptable response [1]. When treatment with biologic agent is necessary, anti-TNF agents are typically selected before other biologic agents because of their high efficacy and the preference given to them in the guidelines and in clinical practice [16]. Other biological agents found to be effective following failure of TNF antagonist include tocilizumab, rituximab and abatacept [13].

Our result shows that at recommended dose level drugs are more efficacious if they combine with Mtx as compared to Mtx alone and placebo therapy. Coprescription of Mtx improve the efficacy of TNF blockade but many patients do not tolerate this DMARD [13]. Rituximab with concomitant Mtx is licensed in the United Kingdom for the treatment of RA in patients who have failed to have adequate response to other DMARDs including at least one TNF inhibitors. Abatacept is licensed for use in combination with Mtx in patients who have failed treatment with one or more DMARDs use before a TNF inhibitor [14].

Heterogeneity in metanalysis refers to the variation in study outcomes between studies. The classical measure of heterogeneity is Cochran's Q. Q has low power as a comprehensive test of heterogeneity especially

when the numbers of studies are small and Q has too much power as a test of heterogeneity if the numbers of studies are large. I2 statics describe the percentage of variation across studies that are due to heterogeneity rather than chance. Unlike Q it does not depend upon the number of studies considered. Our metanalysis result showed majority of all drugs at all dose level suggested significant heterogeneity [17].

CONCLUSION

Among the biological response modifiers anti-TNF inhibitors are highly effective and more efficacious if combine with methotrexate for treatment of rheumatoid arthritis and among them priority given to etanercept.

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