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INFECTIONS ASSOCIATED WITH BIOLOGIC THERAPY: A CLINICAL META-ANALYSIS STUDY

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Keywords:

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ABSTRACT: With the popularity of biologics, treatment for several inflammatory diseases has improved significantly. Biologics are a group of drugs obtained from biological sources that primarily function by suppressing part of the host immune system. However, this process comes at a cost, as it has been reported that the use of biologics carry a major risk in the form of tuberculosis. To verify this claim, a meta-analysis of biologic therapy *vs*. placebo therapy was designed to test biologics of different inflammatory diseases and check for tuberculosis as their side effect. This test included psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis. It was found that biologics used in treating these diseases were mainly responsible for the spread of tuberculosis as a side effect. By mining different databases for literature mentioning biologics that qualify clinical trials and checking for heterogeneity for each study, primary measures were tested for each disease to determine the spread of tuberculosis when treated with these compounds. Meta-analyses were conducted for the study of each disease separately. It was found that for ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis the null hypothesis Ho:μ=0 can be rejected. All primary measures showed statistically significant results for the spread of tuberculosis infection. Therefore, it can be concluded that biologics used to treat these inflammatory diseases may be spreading infections in the form of tuberculosis.

INTRODUCTION: Biologics are a group of drugs developed in the early 1980's that are obtained from biological sources which primarily function by suppressing part of the host immune system [1]. Biologic compounds are heavily used to diagnose, prevent, and treat human diseases and inflammatory conditions.

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Biologics vary from traditional pharmaceutical drugs in various aspects, such as size, heterogeneity, and characterization [2]. Thus, biologics development is costly and difficult due to intensive engineering and manufacturing requirements.

However, biologics remain effective and are the preferred therapeutic mode when treating severe diseases. One of the most successful and growing classes of biologics is monoclonal antibodies, proteins secreted by white blood cells that protect the body from foreign invaders. Whenever pathogens express antigens, the antibody immediately triggers an immune response which

helps the body ward off the invader. Similar to antibodies, therapeutic monoclonal antibodies are produced from living organisms and engineered to work against a particular antigen concerning the disease [3]. Due to the precision during engineering, therapeutic monoclonal antibodies often produce results similar to the human immune response when combating antigens. Due to the growing use of new immune-modulating therapies, comprehending the infectious complications associated with it is even more important, mainly the risk of tuberculosis and herpes zoster [4, 5]. In this study, the aim was to identify the association of these agents with different infections through meta-analysis. Many immune-modulating drugs are still spreading infections in patients and are untested. Thus, the main objective was to target biologics that could cause tuberculosis as the side effect for different diseases. For this study, literature published between 2009 and 2021 were selected from PUBMED, EMBASE and Cochrane central library.

MATERIALS AND METHODS:

Extraction of Data, Selection and Characteristics of Studies: The data were collected from clinical trial organization website (clinicaltrial.org) with the help of specific keywords "ankylosing spondylitis", "Crohn's disease", "adalimumab", "psoriasis", "infliximab", "etanercept", "ulcerative colitis", "rheumatoid arthritis", "psoriatic arthritis" containing placebo-controlled study. The titles and abstract of each study for each disease were inspected for the criteria mentioned above. The selection criteria based on which the studies were included were that the selected studies should be completed, the involved treatment should be the biologics causing tuberculosis as side effect compared to the placebo, and that the patients included in the studies should have the diseases selected for this study. Exclusion criteria was set based on certain conditions, such as the patient should not have active tuberculosis, hepatitis B or hepatitis C, or have previous anti-TNF therapy. The patient should not have any history of demyelinating disease, multiple sclerosis or cancer. After applying these criteria the number of studies selected were [8] in ankylosing spondylitis, [6] in Crohn's disease, [7] in psoriasis, [8] in psoriatic arthritis, 5 in rheumatoid arthritis, [6] in ulcerative colitis. The baseline characteristics of patients were studied. Total 4392 patients of ankylosing spondylitis out of 8 studies [6, 7, 8, 9, 10, 11, 12, 13], 2992 patients of Crohn's disease out of 6 studies [14, 15, 16, 17, 18], 2648 patients of Psoriasis out of 7 studies [19, 20, 21, 22, 23, 24, 25], 3046 patients of Psoriatic Arthritis out of 8 studies [26, 27, 28, 29], [30, 31, 32, 33], 1176 patients of Rheumatoid Arthritis out of 5 studies [34, 35, 36, 37, 38], 1487 patients of Ulcerative Colitis out of 6 studies [39, 40, 41, 42, 43, 44]. The heterogeneity of studies was checked using $\chi 2$ and I2 index statistics. Funnel plot was used for the efficacy measure of publication bias.

The required data were extracted from various studies and divided into two groups; experiment group (biological therapy) and the control group (placebo therapy) for meta-analysis; the baseline characteristics are tabulated in **Table 1**. The data extracted were the name of the study, number of patients, year, age, study design, and biologics level. The primary endpoint measures were that the biological therapy should favor experiments that indicate the possibility of tuberculosis as a side effect in these diseases' biologics.

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS WITH ANKYLOSING SPONDYLITIS, CROHN'S DISEASE, PSORIASIS, PSORIATIC ARTHRITIS, RHEUMATOID ARTHRITIS AND ULCERATIVE COLITIS

Disease	Study	No. of patients	Year	Age (Years)	Study design	Therapy Period	Dosage Regimen	Intervention
Ankylosing spondylitis	Abbott	315	2011	42.2 (11.57)	Double blind	12 weeks	40 mg/week	Adalimumab
	Wyeth	566	2012	40.76 (11.86)	Double blind	16 weeks	50 mg/week	Etanercept
	Centocor Inc.	356	2013	39.3 (12.06)	Double blind	24 weeks	100 mg/4 weeks	Golimumab
	Pfizer	1715	2015	43.9 (12.9)	Cohort	52 weeks	50mg/week	Etanercept
	Novartis	60	2015	42.8 (9.88)	Double blind	28 weeks	0.1mg/kg/3 weeks	AIN457
	AbbVie	789	2013	49.3 (13.3)	Case-only	13 month	--	Humira
	Celgene Corp.	490	2019	44.7 (12.18)	Double blind	24 weeks	30 mg /week	Apremilast
	Merck & Sharp &	101	2019	44.4 (12.9)	Open label	12 months	50 mg/month	GLM

	Dohme Corp							
Crohn's disease	Otsuka Ph.	235	2009	40.9 (12.8)	Double blind	12 weeks	10 sessions	Adacolumn
	UCB Pharma	539	2011	37.67 (12.19)	Double blind	26 weeks	400mg/2 weeks	CertolizumabPegol
	UCB Pharma	40	2015	31.7 (9.7)	Open label	6 weeks	400mg(5 doses 4-weekly)	CertolizumabPegol
	Abbott	188	2011	13.6 (2.49)	Double blind	52 weeks	40 mg/week	Adalimumab
	Janssen Biotech	297	2015	36.3 (12.96)	Double blind	200 weeks	5mg/kg/8 weeks	Infliximab
	AbbVie	1693	2014	35.5 (11.7)	Cohort	24 weeks	--	Humira
Psoriasis	Wyeth	720	2010	45.03 (11.85)	Open label	12 weeks	50 mg twice weekly	Etanercept
	Wyeth	69	2013	45.84 (11.57)	Open label	24 weeks	50 mg/week	Etanercept
	Abbott	147	2011	44.2 (12.82)	Open label	24 weeks	80 mg/week	Adalimumab
	Pfizer	197	2012	96	Double blind	12 weeks	15 mg twice daily	CP-690,550
	Pfizer	171	2015	49.08 (13.96)	Open label	52 weeks	50 mg/week	Etanercept
	AbbVie	500	2014	500	Prospective	12 months	--	Adalimumab
	Celgene Corp.	844	2016	46.0 (12.95)	Double blind	16 weeks	30 mg twice daily	Apremilast
	Wyeth	753	2009	46.52 (11.40)	Double blind	12 weeks	50 mg weekly	Etanercept
	Centocor Inc.	146	2013	48.7 (10.97)	Double blind	12 weeks	90 mg/week	Ustekinumab
	Bristol Myers Squibb	170	2012	52	Double blind	169-729 days	--	Abatacept
Psoriatic arthritis	Novartis	42	2015	47.0 (10.2)	Double blind	10 mg/kg on day 1 and 22	169 days	AIN457
	UCB Pharma	409	2016	47.6 (11.4)	Double blind	400mg twice weekly	48 weeks	CertolizumabPegol
	Celgene Corp.	504	2016	50.4 (11.66)	Double blind	30 mg twice daily	5 years	Apremilast
	Novartis	606	2016	552	Double blind	150 mg	24 weeks	Secukinumab
	Eli lilly& company	417	2017	49.52 (11.87)	Double blind	160 mg of 2 SC injections	24 weeks	Ixekizumab
Rheumatoid arthritis	Abbott	619	2011	402	Double blind	52 weeks	40 mg / week	Adalimumab
	Novartis	80	2012	46.9 (16.22)	Double blind	12 weeks	600 mg on day 1,15,43	Canakinumab
	Incyte Corp.	50	2015	54.9 (11.23)	Double blind	28 days	50 mg once daily	INCB018424
	Abbott	334	2012	54.0 (13.15)	Double blind	52 weeks	40 mg SC/ week	Adalimumab
	Mitsubishi Tanabe Pharma Corp.	93	2014	27	Double blind	12 weeks	100 mg twice daily	MP-435+Methotrexate
Ulcerative colitis	Centocor Inc.	60	2013	13.4 (3.10)	Open label	54 weeks	5 mg/kg every 12 weeks	Infliximab
	Valeant Ph. Int,Inc.	410	2014	43.6 (13.6)	Double blind	8 weeks	9mg every day+3 Entocort	Budesonide-MMX
	Valeant Ph. Int,Inc.	489	2014	42.7 (12.8)	Double blind	8 weeks	9 mg every day+2 Asacol	Budesonide-MMX
	Pfizer	195	2013	110	Double blind	8 weeks	15 mg twice daily	CP-690,550

AbbVie	273	2014	42.7 (14.38)	Double blind	221 weeks	160 mg on day 1,80 mg at week 2, 40 mg /week	Adalimumab
GW Research Ltd	60	2015	43.77(13.90)	Double blind	10 weeks	from 4 to 50 1-5 capsules twice daily	GWP42003

Statistical Analysis: Meta-analysis was performed for assessing between the treatment group and control group. Odds ratio and confidence interval were graphically represented with the help of forest plots, while funnel plots deputed publication biases. Radial and QQ normal plots were used to represent numerical values such as angle and for showing the normal distribution of studies.

Heterogeneity was calculated using χ^2 and I^2 index statistics, the effect size measurement using odds ratio, and the confidence interval, odds ratio, and p-value were calculated for individual study. R software was used for statistical analysis and metafor package [45] was used to calculate the estimated result. With the help of the studies collected, biological therapy was compared against placebo treatment.

It was seen that the result favors experiments showing tuberculosis as a side effect in the biologics using the metafor package. The tool makes use of various parameters, which are described as follows. Effect size, which is a computable determination of robustness of occurrence. *Escalc* function was used to calculate the effect size or outcome measure. The result was *yi* (observed value of the effect size or outcome measure in the studies) and *vi* (corresponding sampling variance) for each disease. Odds ratio (OR) was calculated with the help of Mantel-Haenszel Method, which is a process that creates an evaluation of an association between an exposure and an outcome after modifying for or taking stagger into account. The formula for OR can be represented as

$$\text{Or (MH)} = a \times d / t / c \times b / t$$

In which *a* and *c* are the number of events and total of experiments, *b* and *d* are the number of events and total of control, *t* is the total of all study. 95% confidence interval was used for this analysis, where confidence interval (CI) is a type of interval approximation of a population. If an equivalent hypothesis test is performed, the confidence level accompanies the significance level, i.e. a 95% confidence interval indicates a significance level of 0.05. P-value is the probability of acquiring a result uniform to or maximum than what is actually noticed when the null hypothesis is true. Z-value (absolute value) shows the distance between the raw score and the population means in standard deviation units. μ and σ are the mean and standard deviation of the population, respectively.

These parameters were calculated for studies of each diseases separately. *forest()* function was used to create the forest plot in R. Forest plot is the graphical representation of a meta-analysis which is generally escorted by a table with a list of authors and year of the studies which are taken in doing the meta-analysis.

A funnel plot, a scatter plot of treatment effect against a measure of study precision, was used to check biasness and systematic heterogeneity. When a symmetrical funnel shaped appear from a courteous data set, it is accounted that there are no publication biases. *Funnel* function was used to see the biasness in R. Heterogeneity was present in the selected studies, so a fixed effect model was used. Besides these, radial plots, which is a method to evaluate the stability of discovered result that have varying precisions was used to plot inverse of standard errors on horizontal axis against the individual discovered result systemized by their respective standard errors on vertical axis (i.e., $yi=\sqrt{vi}$) in fixed effect model [42]. Q-Q normal plots were also generated, which display the theoretical quantiles of a normal distribution on the horizontal axis against the observed quantiles of the externally systemized residuals on the vertical axis 42.

RESULTS:

Ankylosing Spondylitis: Biologic therapy comparison was done with placebo therapy. It was seen that the result favors the experiment as compared to placebo [OR=0.8962, 95%CI=0.83-

0.97, P-value>0.005] **Fig. 1A**. heterogeneity was calculated [χ^2=21.53, I^2=64.28%]. No such publication bias is seen **Fig. 1B**. Radial plot plots the value of numeric as angle of radians **Fig. 1C.** Also, the QQ plot shows that the data is normally distributed **Fig.1D.**

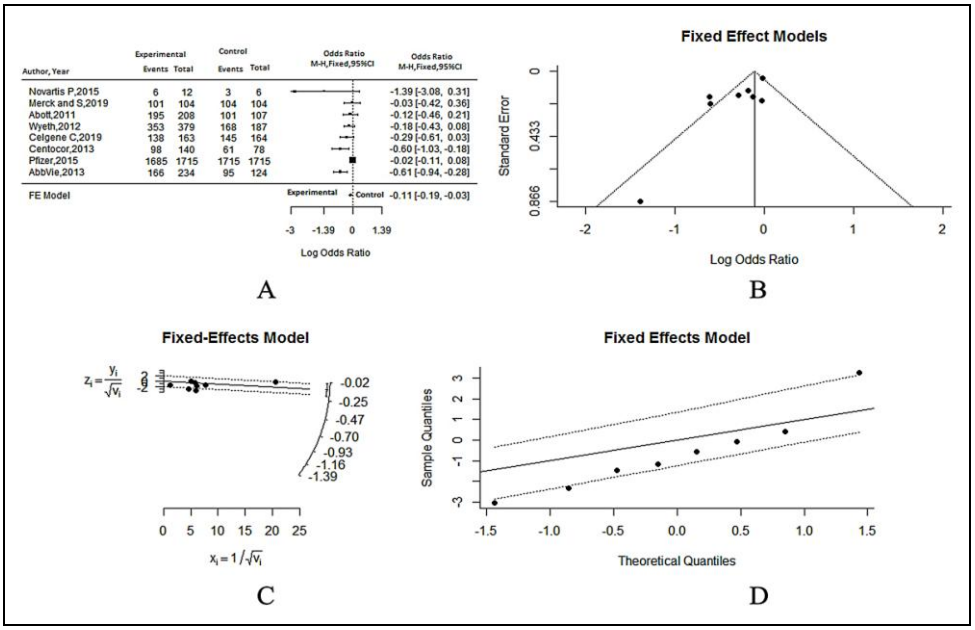

FIG. 1: (A) FOREST PLOT, (B) FUNNEL PLOT, (C) RADIAL PLOT AND (D) QQ PLOT FOR ANKYLOSING SPONDYLITIS

Crohn's disease: Biologic therapy comparison was done with placebo therapy. The result was seen to favor the experiment as compared to the placebo [OR=0.82, 95%CI=0.76-0.89, P-value <0.0001]. **Fig. 2A**. Heterogeneity was calculated [χ^2=122.29, I^2=96.71%]. No such publication bias is seen **Fig. 2B.** Radial plot plots the value of numeric as angle of radians **Fig. 2C**. Also, the QQ plot shows that the data is normally distributed **Fig. 2D.**

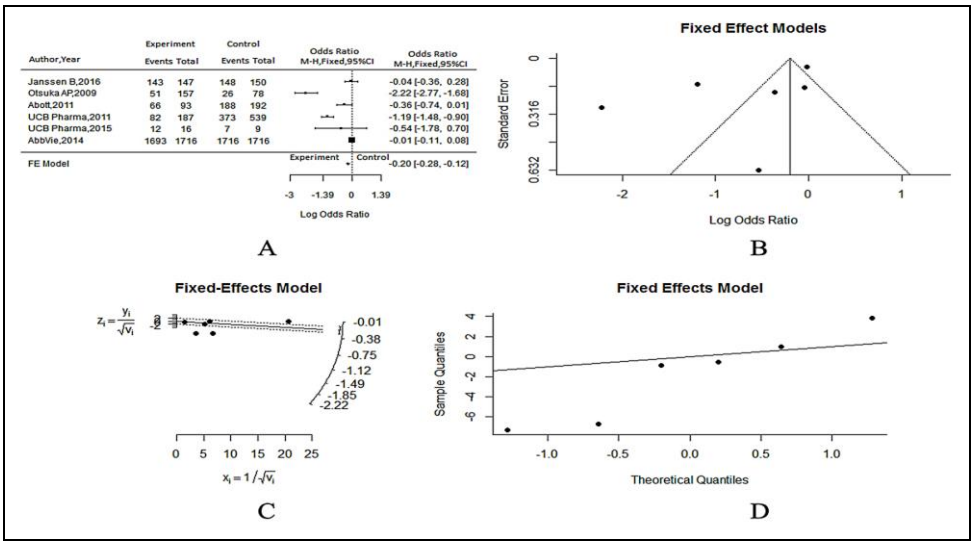

FIG. 2: (A) FOREST PLOT, (B) FUNNEL PLOT, (C) RADIAL PLOT AND (D) QQ PLOTFOR ANKYLOSING SPONDYLITIS CROHN'S DISEASE

Psoriasis: Biologic therapy comparison was done with placebo therapy. It was seen that the result favors experiment as compared to placebo [OR=0.72, 95% CI=0.65-0.79, P-value<0.0001] **Fig. 3A**. Heterogeneity was calculated [χ^2=21.68, I^2=70.04%]. No such publication bias is seen **Fig. 3B**. Radial plot plots the value of numeric as angle of radians **Fig. 3C**. Also, the QQ plot shows that the data is normally distributed **Fig. 3D.**

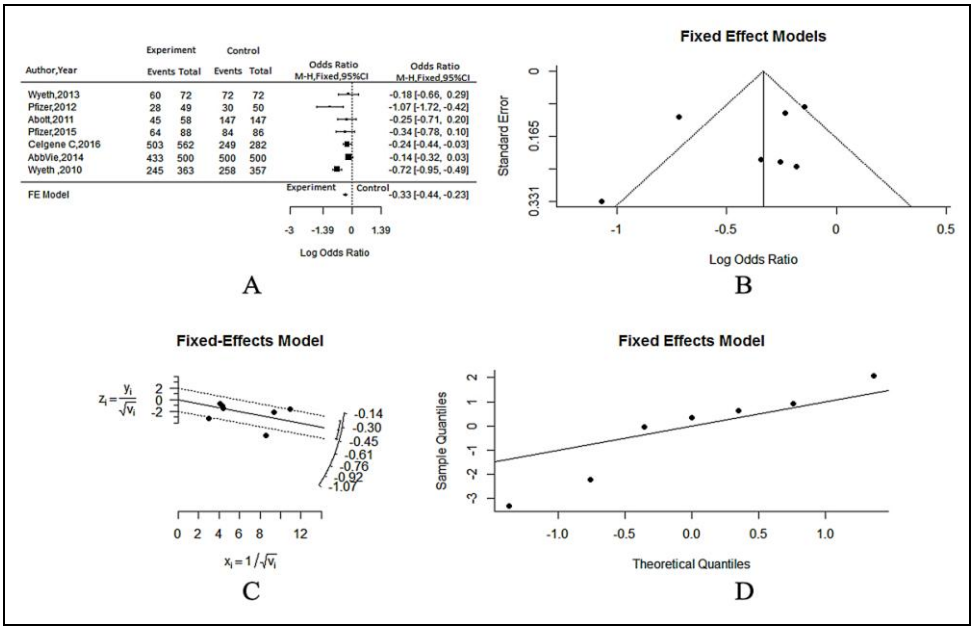

FIG. 3: (A) FOREST PLOT, (B) FUNNEL PLOT, (C) RADIAL PLOT AND (D) QQ PLOT FOR ANKYLOSING SPONDYLITIS PSORIASIS

Psoriatic Arthritis: Biologic therapy comparison was done with placebo therapy. It was seen that the result favors the experiment as compared to placebo [OR=0.77, 95% CI=0.68-0.87, P-value<0.0001] **Fig. 4A**. Heterogeneity was calculated [χ^2=3.10, I^2=0%]. No such publication bias is seen **Fig. 4B**. Radial plot plots the value of numeric as angle of radians **Fig. 4C**. Also, the QQ plot shows that the data is normally distributed **Fig. 4D.**

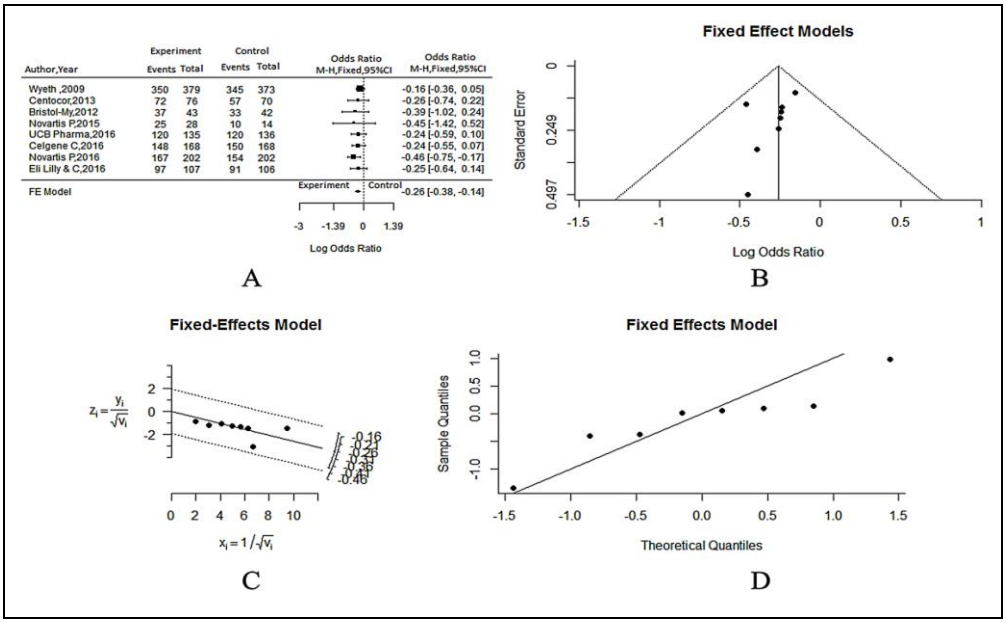

FIG. 4: (A) FOREST PLOT, (B) FUNNEL PLOT, (C) RADIAL PLOT AND (D) QQ PLOT FOR ANKYLOSING SPONDYLITIS PSORIATIC ARTHRITIS

Rheumatoid Arthritis: Biologic therapy comparison was done with placebo therapy. It was seen that the result favors the experiment as compared to placebo [OR=0.65, 95% CI=0.53-0.79, P-value<0.0001] **Fig. 5A**. Heterogeneity was calculated [χ^2=11.29, I^2=37.61%]. No such publication bias is seen **Fig. 5B**. Radial plot plots the value of numeric as angle of radians **Fig. 5C**. Also, the QQ plot shows that the data is normally distributed **Fig. 5D.**

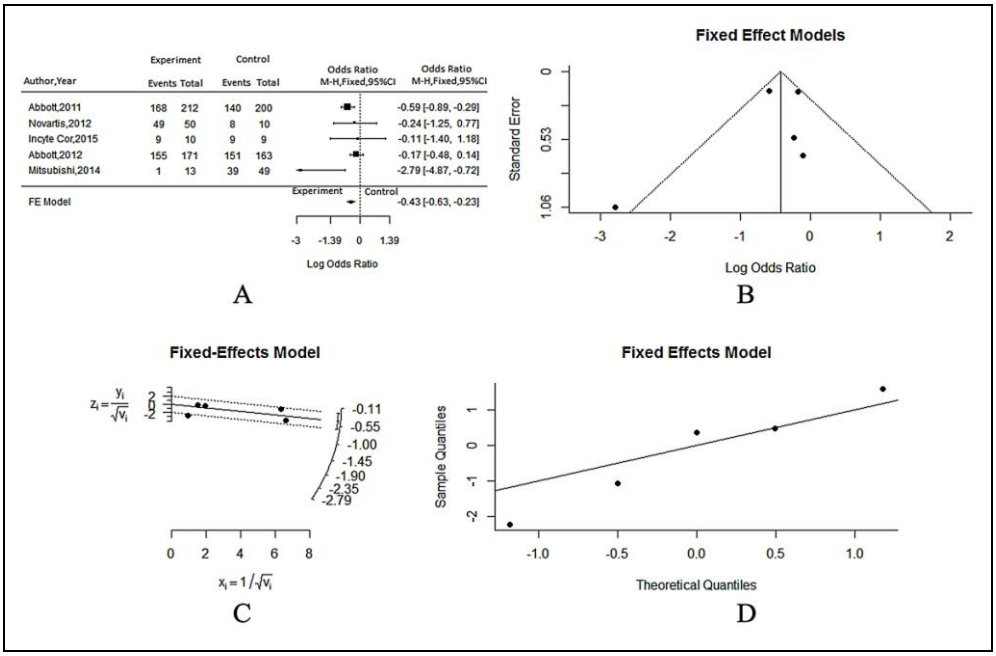

FIG. 5: (A) FOREST PLOT, (B) FUNNEL PLOT, (C) RADIAL PLOT AND (D) QQ PLOT FOR RHEUMATOID ARTHRITIS

Ulcerative Colitis: Biologic therapy comparison was done with placebo therapy. It was seen that the result favors experiment as compared to placebo [OR=0.45, 95% CI=0.36-0.56, P-value<0.0001] **Fig. 6A**. Heterogeneity was calculated [χ^2=12.05, I^2=0%]. No such publication bias is seen **Fig. 6B**. Radial plot plots the value of numeric as angle of radians **Fig. 6C**. Also, the QQ plot shows that the data is normally distributed **Fig. 6D.**

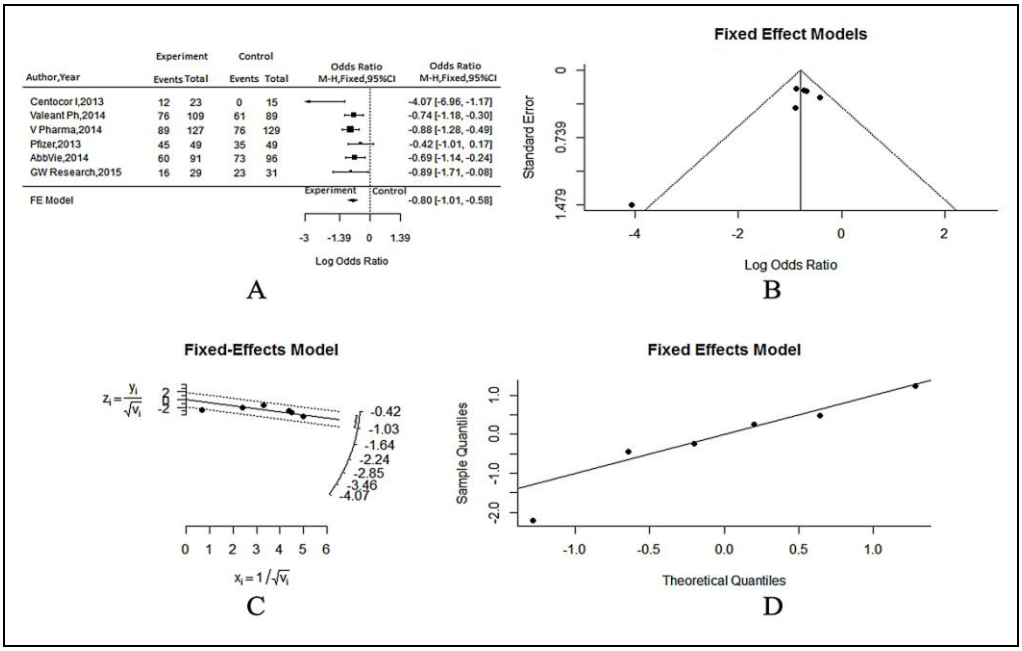

FIG. 6: (A) FOREST PLOT, (B) FUNNEL PLOT, (C) RADIAL PLOT AND (D) QQ PLOT FOR ULCERATIVE COLITIS

CONCLUSION: A meta-analysis of biological therapy *vs.* placebo therapy is done for disease like ankylosing spondylitis, Crohn's disease, psoriasis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis with different study group of each disease to see the side effect caused by the biologics of these diseases. After meta-analysis, it can be seen that the result follows the experiment which can be concluded that the biologics of each disease gives side effect of tuberculosis. End-point measures for each diseases is estimated. The study is grouped as biologic therapy and placebo therapy.

A comparison between both groups gave a statistically significant result. The P-value for each endpoint measures ankylosing spondylitis (P>0.005), Crohn's disease (P<0.0001), psoriasis (P<0.0001), psoriatic arthritis (P<0.0001), rheumatoid arthritis (P<0.0001), ulcerative colitis (P<0.0001) which is less than 0.05.

Publication bias was also checked with the help of a funnel plot. No such publication bias was found in each disease. This meta-analysis might contain many limitations due to search strategy applied, inclusion and exclusion criteria of studies and publication bias. Different protocols were developed to extract data from studies and analyze those data. But a vigorous strategy is applied for meta-analysis and it will help in fortune for clinical trial in biologics giving tuberculosis as side effects.

The prominence of this study was to find the side effects that can be caused by the biologics of diseases like, ankylosing spondylitis, Crohn's disease, psoriasis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis. Finally, a meta-analysis of a clinical trial is applied, showing that the biologics have side effects. Therefore, it can be concluded that the biologics of diseases like ankylosing spondylitis, Crohn's disease, psoriasis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis give tuberculosis as side effects.

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