

SYSTEMATIC REVIEW OF INFECTION RISKS AMONG RHEUMATOID ARTHRITIS PATIENTS RECEIVING BIOLOGIC AGENTS

Sidney Erwin T. Manahan, M.D. and Eric Jason B. Amante, M.D.

ABSTRACT

Infection is one of the leading causes of mortality among patients with rheumatoid arthritis (RA). Several RA cohorts have recently confirmed this increased risk of infection with relative risks ranging from 5.3 to 14.9. This predisposition to infections results from an interplay of disease-associated and treatment-associated factors. The introduction of biologic response modifiers, also known as biologic agents, in the treatment of RA has roused interest on their impact of the co-morbidities of RA, particularly infections.

Objective: To systematically review safety data from published randomized controlled trials (RCTs) evaluating the use of biologic agents in the management of RA in terms of infection rates documented

Methods: A PUBMED Search from 1999 - October 2005 was performed using the terms rheumatoid arthritis, biologic agents, the specific biologic agents available at that time, and randomized controlled trials. Clinical trials were likewise identified by searching electronic data sources as well as reference lists and conference abstracts. Retrieved studies were independently assessed for quality by the two authors and were eventually included in the quantitative analysis.

Results: Twenty Three (23) studies were retrieved following PUBMED search. Of these, 18 studies of fair quality were included. The general incidence of infection was not increased by the administration of biologic agents [Relative risk 1.01, 95% CI (0.96, 1.07)]. However, serious infections requiring intravenous antibiotic administration or necessitating hospital admission was significantly higher in the group receiving biologic agents [Relative risk 1.35, 95% CI (1.04, 1.75)]. This risk was higher in the groups receiving infliximab.

Conclusion: Biologic agents do not increase the incidence of infections among rheumatoid arthritis patients. However, serious infections occurred more frequently among those who received such therapies.

Studies of higher quality are needed to compare if these treatment-associated risks are higher than that observed with traditional disease modifying agents.

INTRODUCTION

Infection is a major cause of morbidity and mortality among patients with RA. Earlier studies on outcomes of RA showed infection accounting for one-fourth of deaths. Recently, three independent longitudinal studies reaffirmed that infection was a major contributor to all-cause mortality among RA patients. The risk of developing an infection is increased among RA patients – recent cohorts report relative risks of 5.3 to 14.9 compared to the normal population.²³

Similar to other RA co-morbid conditions, the increased risk of infection is believed to arise from the interplay of disease-specific and treatment-associated factors. Rheumatoid arthritis alters the function of natural killer cells and T-lymphocytes which are important in cell-mediated immunity. Available therapies for RA potentially aggravate this effect on cellular immunity by decreasing the number and function of important cell-mediators. It is believed that this combined effect of immunosuppression is central to the increased risk of infection among RA patients.

The population-based incident cohort of Doran, et al. identified potential risk factors for serious infection in RA patient.²⁴ Increasing age, presence of extra-articular manifestations, leucopenia, presence of other medical co-morbidities (chronic lung disease, alcoholism, organic brain disease and diabetes mellitus) and corticosteroid use were found to be strong predictors of infection. Interestingly, the study found that use of disease modifying anti-rheumatic drugs (DMARDs) was not associated with an increased risk of infection after adjusting for demographic characteristics, co-morbidities and disease related factors in a multivariate analysis.

The availability of infliximab and etanercept in the treatment of RA has generated observations of the effects of these agents on RA co-morbidities,

Reprint request to: Sidney Erwin T. Manahan, M.D., Section of Rheumatology, Department of Medicine, UP-PGH Medical Center, Taft Ave., Manila, Philippines.

particularly infection.²³ Listing, *et al.* reported a higher prior risk of infection among RA patients treated with etanercept and infliximab compared to RA patients receiving traditional DMARDs in their German Biologics Register of 1,529 patients seen from May 2001 to September 2003. Incidence of 22.6 and 28.3 per 100 patient-years were reported for etanercept and infliximab, respectively. This is compared to the 6.8 per 100 patient-years among patients receiving non-biologic DMARDs. Serious infections similarly occurred more in the etanercept (6.4) and infliximab (6.2) treated patients than in those receiving DMARD (2.3) (p value 0.0016). The study suggested that infection risk is increased by treatment with tumor necrosis factor inhibitors.²⁵

This is in contrast to the study of Dixon, *et al.* where treatment with anti-tumor necrosis factor (anti-TNF) therapies were not associated with an increased over-all risk of serious infection compared to DMARDs treatment after adjusting for baseline risk. This was based on a national prospective observational study of 7,664 anti-TNF treated and 1,354 DMARD treated patients seen from December 2001 to September 2005 in the British Society of Rheumatology Biologics Register. The incidence rate ratio (IRR) for serious infections in the anti-TNF treated compared to the DMARD treated cohort was 1.03 (95% confidence interval 0.68, 1.57). However, serious skin and soft tissue infections were increased among anti-TNF treated patients with an IRR of 4.28 (95% confidence interval 1.06, 17.17). No significant difference in incident infections were found among the three biologic agents in the cohort – infliximab, etanercept and adalimumab.²⁶

Estimates of infection risks from randomized controlled trials are generally difficult. Data from these trials have not been powered to detect sparse adverse events such as infections in their analysis and interpretation. A solution to the lack of estimates of infection risk from clinical trials is to pool the results in a meta-analysis. This technique is often used to assess drug efficacy but has been infrequently used to determine harmful effects. Using such a technique applies a validated approach to pooling sparse data as an adjunct in assessing drug safety.

OBJECTIVE

This systematic review aims to determine the risks of developing serious and non-serious infections among RA patients being treated with biologic agents.

MATERIALS AND METHODS

Search Strategy

A MEDLINE Search was performed to identify randomized placebo controlled clinical trials or systematic reviews on the use of biologic agents in the treatment of RA from 1999 to October 2006. This was supplemented by citation tracking in published bibliographies and conference proceedings. The Cochrane Database of Systematic Reviews was likewise searched for existing studies and meta-analysis on biologic agents and RA. The following terms were used in the literature search: biologic agents, Rheumatoid Arthritis, Anti-tumor necrosis factor (anti-TNF) agents and specific names of such agents (e.g. adalimumab, infliximab and etanercept), Interleukin 1 receptor (IL-1R) antagonist and specific names of such agents (anakinra), costimulation blockade and specific names of such agents (abatacept), anti CD20 antagonist and specific names of such agents (rituximab), randomized controlled trial.

Criteria for Inclusion of Studies in the Review

Only randomized controlled trials were considered for inclusion in the systematic review. For studies using a cross-over design, only data from the preliminary phase of the trial were considered to exclude the compounded effect of receiving different forms of treatment.

Patients enrolled in the clinical trials should be adults (aged 18 – 70 years old) who had been diagnosed with Rheumatoid Arthritis using the 1997 American College of Rheumatology (ACR) Criteria for the Classification of Rheumatoid Arthritis. Baseline characteristics of patients and known prognostic factors for infections should be comparable between groups (p>0.05)

Only studies with at least two treatment groups were to be included – one group should have been randomized to receive a biologic agent for at least 12 weeks duration. The following biologic agents were considered in this systematic review: anti-TNF agents (Adalimumab, Infliximab and Etanercept), interleukin 1 receptor antagonist (Anakinra), costimulatory blocking agents (Abatacept) and anti CD20 antagonist (Rituximab). The comparison group should receive either a placebo or a traditional disease modifying anti-rheumatic drug (DMARD). Aside from the biologic agents, other concomitant treatments in the study groups should be similar.

Included trials should indicate in their safety reports the incidence rates of infections (both serious and non-serious) or at least tabulate the number of infections reported during the clinical trial. For studies wherein only the number of infections is reported, the number of patients assigned to the treatment group will be used as the denominator.

Validity Assessment and Data Analysis

Retrieved trials were independently evaluated by the two authors for bias in the following methodological features: randomization concealment (selection bias), masking of allocation or blinding of physicians and outcome assessors (detection and performance bias), and intention-to-treat analysis (exclusion bias). Disagreements were resolved by consensus.

Abstracted data from included trials were then entered and analyzed using Review Manager (RevMan) version 4.2.9 (version date: October 23, 2006).

RESULTS

Twenty-three journal articles were identified using the search strategy outlined above. Of these, only 18 were included in the final analysis. One study⁹ employed a cross-over design where some patients originally assigned to the placebo group eventually received a biologic agent. No safety report was provided regarding infections documented during the pre-cross-over phase and thus could not be included in the systematic review. In the remaining four excluded trials, there was difficulty abstracting the incidence of infection as the authors separately reported these events (upper respiratory tract infection, sinusitis, pharyngitis) without providing data on the over-all index of infection occurrence.

Of the 18 included trials, 16 were evaluated to be of fair quality – mostly because randomization concealment was not ensured in the description of the study protocol. Only two studies were of good quality – both were for anti-TNF agents.

The included trials enrolled a total of 11,323 adult rheumatoid arthritis patients receiving treatment for a duration of four to 24 months. Table 1 tabulates the number of patients enrolled in included trials stratified based on the biologic agent studied. The numbers listed below reflect a frequently used design in clinical trials of randomizing more patients to the active treatment group - usually in the ratio of 2:1.

Table 1. Population of Patients Enrolled in the Different Trials Stratified Base on Biologic Agent Studied

Biologic Agent	# of Trials	# Randomized to Study Agent	# Randomized to Placebo Group	Total Number
Abatacept	4	1,527	766	2,293
Etanercept	3	1,236	498	1,734
Infliximab	3	1,814	747	2,561
Adalimumab	3	1,170	519	1,689
Anakinra	2	1,366	534	1,900
Rituximab	3	748	398	1,146
All agents	18	7,861	3,462	11,323

Aside from the diagnosis of RA, patients included in the trials were assessed to have active disease based on criteria using a combination of joint counts (swollen and tender), laboratory values (erythrocyte sedimentation rate or C-reactive protein), or clinical features (duration of morning stiffness). Likewise, some studies indicated that included patients should either be class I, II or III of the American College of Rheumatology Revised Criteria for Classification of Global Functional Status in Rheumatoid Arthritis (1991).

Infection Risk Among Patients Treated with Biologic Agents (See Figure 1)

Only 13 trials reported the over-all incidence of infection for the duration of their study period. The data from 8,463 enrolled patients showed that the over-all risk of infection among RA patients were not significantly increased by the administration of biologic agents [Relative risk 1.03 95% CI (0.99, 1.09)]. The chi-square test for heterogeneity of the studies did not reach statistical significance, indicating that across these trials the results are comparable.

Furthermore, if the results are stratified based on the mechanism of action of the biologic drug TNF blocking agents, interleukin 1 receptor antagonist, costimulatory blocking agents and anti-CD20 antagonist, it likewise appears that there is no difference in terms of infection risk between these groups. However, this result should be taken with caution, as none of the trials on infliximab had indicated the incidence of non-serious infections – and this group represents almost one-quarter of the total number of patients included in the quantitative analysis.

Risk of Serious Infection among Patients Treated with Biologic Agents (See Figures 2 and 3)

Most of the included trials reported their incidence of serious infections, defined as infection requiring either intravenous antibiotic administration or necessitating hospitalization for treatment. Data from 11,323 enrolled patients show that serious infections were significantly higher among biologics-treated patients. [Relative risk 1.35 95%CI (1.04, 1.75)]. The test for heterogeneity was not significant indicating comparable results between the studies. However, grouping these trials based on the biologic agent used, serious infections occurred more frequently among patients treated with infliximab [Relative risk 1.70 95% CI (1.05, 2.76)] compared to other biologic agents. However, grouping these trials based on the mechanism of action of the agent used, serious infections tended to occur more frequently among patients treated with TNF-blocking agents [Relative risk 1.29] but this difference did not reach statistical difference. These results may suggest that the increased risk of serious infection may be drug specific rather than a class effect.

Implications On Further Research and Practice

For most of the studies included in this systematic review, the primary endpoint was an evaluation of the efficacy of these biologic agents in improving the rheumatic complaint and functional disability. Few of these trials were specifically aimed at evaluating the safety of biologic agents among RA patients. This may translate to these trials not being powered to detect differences in infections among treatment groups. More studies looking specifically into safety of these biologic agents are recommended.

The results of the systematic review should not deter physicians from using these very effective drugs in the treatment of RA. Instead, the results should be a reminder to be vigilant in monitoring for infections particularly in this subset of patients.

CONCLUSION

Biologic agents do not significantly predispose RA patients to more infections. However, serious infections occurred more frequently among those who received such therapies. Studies of higher quality

are needed to compare if these treatment-associated risks are higher than that observed with traditional disease modifying agents.

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Figure 1

Review: Infection among Rheumatoid Arthritis patients receiving biologic therapy
 Comparison: 01 Biologic agents vs Placebo
 Outcome: 01 Infection

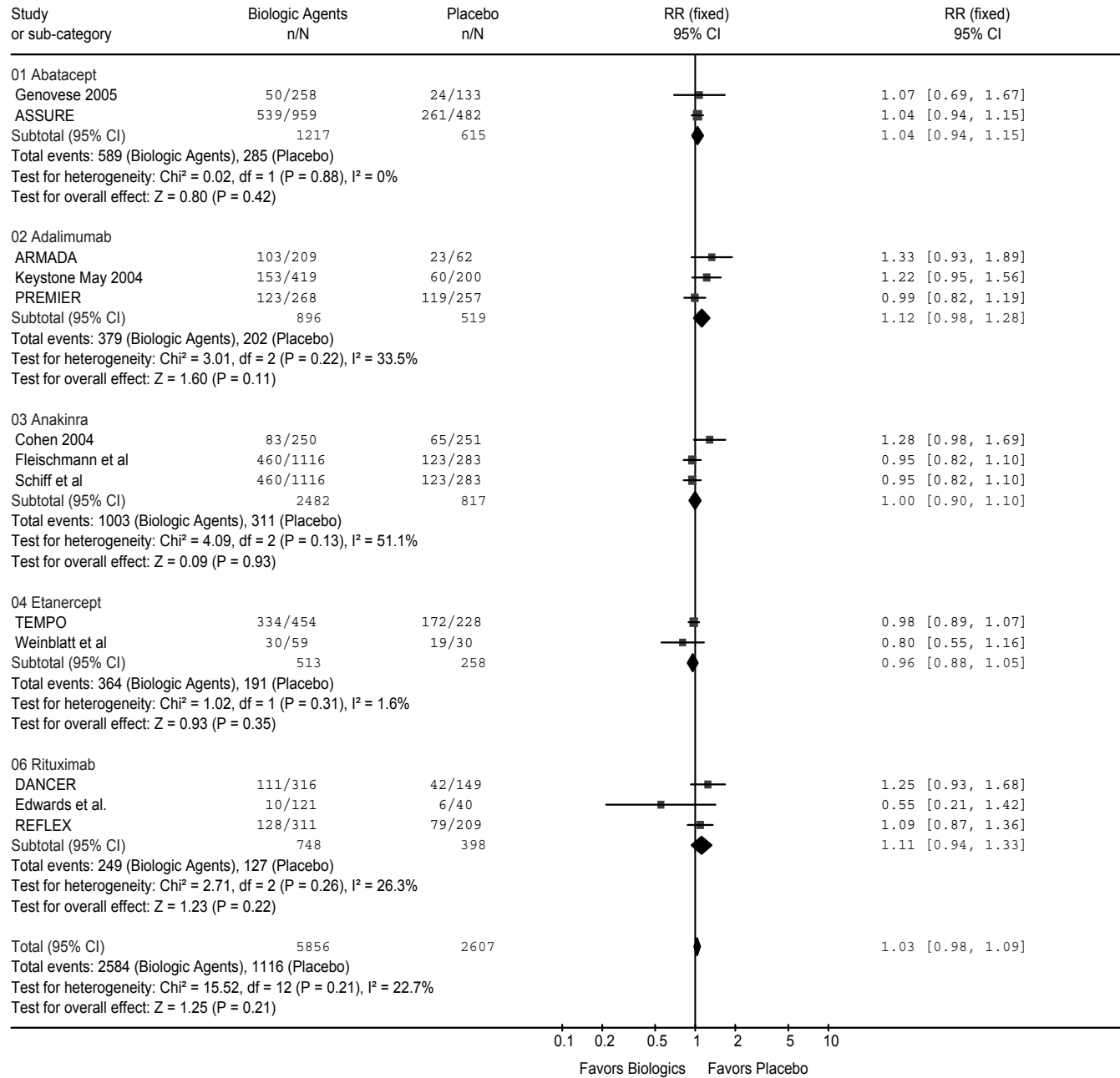


Figure 2

Review: Infection among Rheumatoid Arthritis patients receiving biologic therapy
 Comparison: 01 Biologic agents vs Placebo
 Outcome: 02 Serious Infections

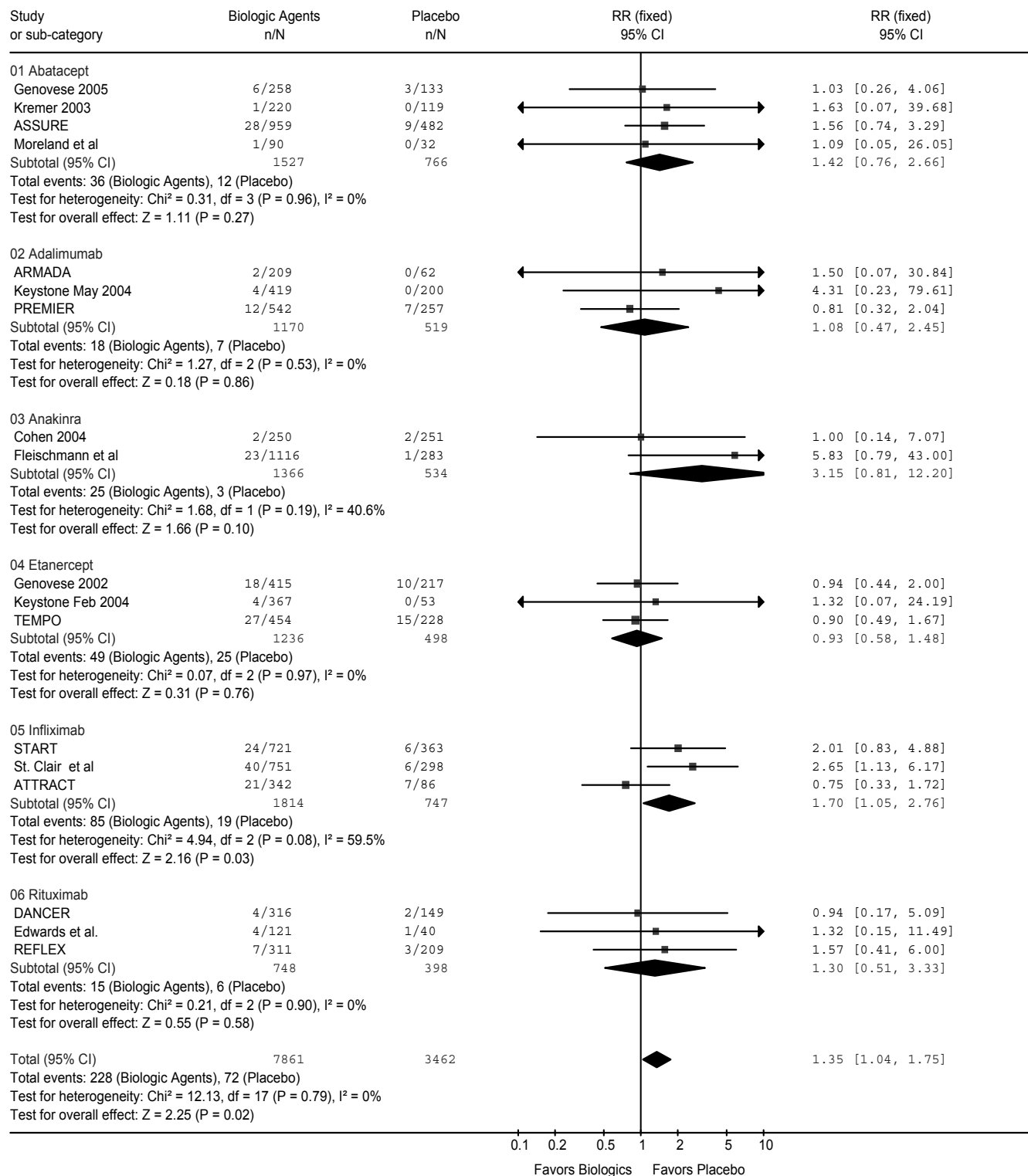


Figure 3

Review: Infection among Rheumatoid Arthritis patients receiving biologic therapy
 Comparison: 01 Biologic agents vs Placebo
 Outcome: 03 Serious infection by MOA

