GOVERNO DO DISTRITO FEDERAL
Secretaria de Estado de Saúde
Fundação de Ensino e Pesquisa em Ciências da Saúde
Escola Superior em Ciências da Saúde
Mestrado Acadêmico em Ciências da Saúde

EFICÁCIA COMPARADA DO RITUXIMAB, ABATACEPT E TOCILIZUMAB EM PACIENTES COM ARTRITE REUMATÓIDE REFRATÁRIA AO METOTREXATO OU AGENTES ANTI-TNF: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE EM REDE

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BRASÍLIA - DF
2021

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Trabalho de Conclusão apresentado ao Programa de Pós-Graduação *Stricto Sensu* em Ciências da Saúde da Escola Superior em Ciências da Saúde, como requisito parcial para obtenção do Título de Mestre em Ciências da Saúde.

Linha de Pesquisa: Estudos Clínicos e Epidemiológicos.

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BRASÍLIA - DF

2021

Catalogação na fonte

Fundação de Ensino e Pesquisa em Ciências da Saúde

Escola Superior de Ciências da Saúde

Biblioteca Central da Fundação de Ensino e Pesquisa em Ciências da Saúde

Oliveira, Amanda Borges de

OO48e Eficácia comparada do rituximab, abatacept e tocilizumab em pacientes com artrite reumatóide refratária ao metotrexato ou agentes anti-tnf: uma revisão sistemática e meta-análise em rede / AmandaBorges de Oliveira; orientador Luiz Sérgio Fernandes de Carvalho. - Brasília, 2021.

89 p.

Dissertação (Mestrado - Programa de Pós-GraduaçãoStricto Sensu em Ciências da Saúde da Escola
Superior em Ciências da Saúde) - Coordenação de Pós-Graduação e Extensão, Escola Superior de Ciências da Saúde, 2021.

1. Artrite reumatóide. 2. Rituximab. 3. Abatacept. 4. Tocilizumab. 5. American College of Rheumatology. I. Carvalho, Luiz Sérgio Fernandes de, orient. II. Título.

TERMO DE APROVAÇÃO

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“Eficácia comparada do rituximab, abatacept e tocilizumab em pacientes com artrite reumatóide refratária ao metotrexato ou agentes anti-tnf: uma revisão sistemática e meta-análise em rede”.

Dissertação aprovada como requisito parcial para obtenção do título de Mestre em Ciências da Saúde pelo Programa de Pós-Graduação Stricto Sensu em Ciências da Saúde da Escola Superior em Ciências da Saúde/FEPECS.

Aprovada em: 21/09/2021

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Dados: 2021.10.03 22:25:11 -03'00'

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Brasília, 21/09/2021

Dedico esse trabalho ao meu esposo, meus pais, tios e orientador.
Sem dúvida foram os maiores incentivadores.

Agradecimento

Agradeço imensamente à Deus por me fortalecer diariamente;
Ao meu esposo pela paciência durante essa trajetória;
Aos meus pais e familiares pelo apoio;
Aos meus amigos que perisistiram junto comigo;
Ao meu orientador por acreditar que eu conseguiria;
E a mim mesma, que mesmo em momentos de angústia e desespero não desisti.

RESUMO

Antecedentes: Embora os medicamentos anti-reumáticos modificadores de doenças (DMARD), incluindo os sintéticos, como o metotrexato (MTX), e os biológicos (bDMARD), como os inibidores de fatores de necrose tumoral (agentes anti-TNF), tenham inquestionavelmente melhorado a qualidade de vida dos indivíduos com artrite reumatóide (AR), pelo menos um terço dos indivíduos não responde a estes tratamentos. Rituximab, abatacept, e tocilizumab são opções bDMARD disponíveis, mas não é claro se algum destes medicamentos é superior aos outros.

Objetivo: avaliar eficácia entre rituximab, tocilizumab e abatacept em pacientes com AR refratários ao tratamento com MTX ou anti-TNF, como objetivo geral e revisar sistematicamente a literatura, através de estudos clínicos randomizados e comparar indiretamente os tratamentos para AR entre rituximab, tocilizumab e abatacept; avaliar o impacto dos tratamentos para AR com rituximab, tocilizumab e abatacept sobre a resposta ACR, como objetivos específicos.

Fontes de dados: MedLine (PubMed), Cochrane Library, Embase, Web of Science, Scopus, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e Literatura Cinzenta (Opengrey e Google Acadêmico) até a data de 18 de julho de 2020.

Seleção do estudo: Fase 2, 3 ou 4 RCT avaliando pacientes com artrite reumatoide refratária ao tratamento com anti-TNF ou MTX, tratados com Rituximab, Abatacept e Tocilizumab (grupo teste) em comparação com os que não foram tratados (grupo controle).

Extração de dados: As características, qualidade e dados do estudo foram avaliados independentemente por 2 revisores. O desfecho primário foi a redução de 70% na atividade da doença, conforme critério de resposta da American College of Rheumatology (ACR70). A revisão foi registrada na base International Prospective Register of Systematic Reviews do Centre for Reviews and Dissemination / University of York (PROSPERO). Número do registro: CRD42020167953

Síntese de dados: A meta-análise incluiu 19 RCTs, com 7.835 pacientes aleatorizados para os braços de intervenção versus braços controle e uma duração média de estudo de 1,2 anos. A idade média foi de 52,3 anos, 77,2% dos indivíduos eram mulheres, e a duração média da doença foi de 8,7 anos. Os medicamentos rituximab, tocilizumab e abatacept foram comparados com placebo em 13 ensaios

clínicos e com comparador ativo (anti-TNF) em 6 ensaios clínicos como tratamento adjuvante. O *Hazard Ratio* (HR) para se conseguir uma resposta ACR70 aos seis meses não foram diferentes entre os bDMARDs quando comparados com placebo, no entanto, houve uma elevada heterogeneidade. Foram identificados três fatores que evidenciavam um desequilíbrio crítico entre as classes bDMARD: escore HAQ (*Health Assessment Questionaire)* basal, duração do estudo, e frequência do tratamento anti-TNF no braço controle. Estas variáveis explicativas foram escolhidas em função de sua associação com a resposta ACR70 em regressões univariadas e da presença de desbalanço entre os braços de tratamento em relação a estas características. Para melhor compreender a heterogeneidade entre as RCTs, foram realizadas meta-regressões multivariadas ajustadas a estes três fatores para o risco relativo (RR) para alcançar uma resposta ACR70 durante o seguimento do estudo. Assim, a heterogeneidade foi atenuada (I^2 = 24%, p para heterogeneidade = 0,27) e o poder explicativo do modelo aumentou (R^2 = 85%). Neste modelo, rituximab não modificou a hipótese de obter uma resposta ACR70 em relação ao abatacept (RR = 1,773, 95% CI 0,113-10,21, p = 0,765). Por outro lado, o abatacept foi associado com um RR = 2,217 (95% CI 1,554-3,161, p < 0,001) para ACR70 em comparação com o tocilizumab.

Conclusão: Na meta-análise em rede não houve diferença significativa entre tocilizumab, abatacept e rituximab para atingir resposta ACR70, havendo baixa inconsistência, mas elevada heterogeneidade entre os estudos. A partir do resultado de metarregressões multivariadas, se as condições dos RCTs fossem semelhantes, estimamos que o abatacept aumentaria em 2,22x a chance de atingir a resposta ACR70 em comparação com tocilizumab.

Palavras-chave: Artrite reumatóide, rituximab, abatacept, tocilizumab, American College of Rheumatology, meta-análise, meta-regressão.

ABSTRACT

Background: Although disease-modifying antirheumatic drugs (DMARD), including synthetic ones, such as methotrexate (MTX), and biological ones (bDMARD), such as tumor necrosis-factor inhibitors (anti-TNF agents), have unquestionably improved the quality of life of individuals with rheumatoid arthritis (RA), at least one third of individuals do not respond to these treatments. Rituximab, abatacept, and tocilizumab are bDMARD options available, but it is unclear whether any of these drugs is superior to the others.

Objective: To compare the efficacy of rituximab, tocilizumab, and abatacept in individuals with RA refractory to treatments with MTX or anti-TNF agents as general objectives and to systematically review the literature through randomized clinical trials and indirectly compare treatments for RA between rituximab, tocilizumab and abatacept; to evaluate the impact of treatments for RA with rituximab, tocilizumab and abatacept on ACR response as specific objectives.

Data sources: PubMed, Cochrane Library, Embase, Web of Science, Scopus, LILACS and Gray Literature (Opengrey and Academic Google) until July 18, 2020.

Study selection: Phase 2-4 randomized controlled trials (RCTs) evaluating patients with RA refractory to MTX or anti-TNF therapy treated with rituximab, abatacept, and tocilizumab (intervention arm) compared to controls.

Data extraction: Study characteristics, quality, and data were independently assessed by two investigators. The primary outcome was a 70% reduction in disease activity according to the American College of Rheumatology response criteria (ACR70). A revisão foi registrada na base International Prospective Register of Systematic Reviews do Centre for Reviews and Dissemination / University of York (PROSPERO). Número do registo: CRD42020167953.

Data synthesis: The meta-analysis included 19 RCTs, with 7,835 patients randomized to the intervention vs. control arms and a mean study duration of 1.2 years. The mean age was 52.3 years, 77.2% of individuals were women, and the mean disease duration was 8.7 years. The drugs rituximab, tocilizumab and abatacept were compared with placebo in 13 clinical trials and with active comparator (anti-TNF) in 6 clinical trials as adjuvant treatment. The hazard ratios (HRs) for achieving an ACR70 response at six months were not different among the bDMARDs when compared to placebo, however,

there was a high heterogeneity. Three factors showing a critical imbalance among the bDMARD classes were identified: baseline HAQ (*Health Assessment Questionaire)* score, study duration, and frequency of anti-TNF treatment in the control arm. These explanatory variables were chosen based on their association with ACR70 response in univariate regressions and the presence of imbalance between treatment arms with respect to these characteristics. To better understand the heterogeneity among RCTs, multivariate meta-regression adjusted to these three factors were conducted for the relative risk (RR) for achieving an ACR70 response during the study follow-up. Thus, heterogeneity was attenuated (I^2 = 24%, p for heterogeneity = 0.27) and the explanatory power of the model increased (R^2 = 85%). In this model, rituximab did not modify the chance of achieving an ACR70 response compared to abatacept (RR = 1.773, 95% CI 0.113–10.21, p = 0.765). In contrast, abatacept was associated with a RR = 2.217 (95% CI 1.554–3.161, p < 0.001) for ACR70 compared to tocilizumab.

Conclusion: In the network meta-analysis, there was no significant difference among tocilizumab, abatacept, and rituximab in achieving an ACR70 response, there being a low inconsistency, but high heterogeneity among studies. Based on the result of multivariate meta-regressions, if the conditions of the RCTs were similar, we estimate that abatacept could increase the chance of reaching an ACR70 response by 2.2-fold compared to tocilizumab.

Keywords: Rheumatoid arthritis; Rituximab; Abatacept; Tocilizumab; bDMARD; American College of Rheumatology; Network meta-analysis; Meta-regression.

LISTA DE ABREVIATURAS E SIGLAS

ABA	Abatacept
ACR	*American College of Rheumatology*
AINE	anti-inflamatórios não esteroides
ANTI-CCP	Anticorpo Anti-péptido Citrulinado Cíclico
AR	Artrite Reumatóide
CBAF	Componentes Básico da Assistência Farmacêutica
CDAI	*Clinical Disease Activity Index*
CEAF	Componente Especializado da Assistência Farmacêutica
CONITEC	Comissão Nacional de Incorporação de Tecnologias
DMARDS	Drogas antirreumáticas modificadoras da doença
DECS	Descritores em Ciências da Saúde
EULAR	*European League Against Rheumatism*
FR	Fator Reumatóide
GRADE	*Grading of Recommendations Assessment, Development and Evaluation*
HAQ	*Health Assessment Questionaire*
HCQ	Hidroxicloroquina
HIV	Vírus da Imunodeficiência Humana
HR	*Hazard ratios*
LEF	Leflunomida
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
MESH	Medical Subject Headings
MMCD	Medicamentos modificadores do curso da doença
MTX	Metotrexato
PCDT	Protocolos Clínicos e Diretrizes Terapêuticas
PCR	Proteína C reativa
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT	*Randomized controlled trial*

RR	Risco relativo
RTX	Rituximab
SSZ	Sulfassalazina
SUS	Sistema Único de Saúde
TCZ	Tocilizumab
TNF	*Tumour necrosis fator*
VS	Velocidade de sedimentação

Sumário

APRESENTAÇÃO

Este é um momento de extrema alegria, momento no qual alcanço mais um degrau na minha carreira. Finalizo uma etapa sonhada há muitos anos, marcada por desafios e muita dedicação. Desde a graduação em Enfermagem identifiquei-me com a área de pesquisa e apesar de amar a área assistencial, os planos de exercer a atividade de Docência e realizar a Pós-graduação Strictu Senso sempre estiveram muito presentes em minha trajetória.

Formada há 10 anos em Enfermagem pela Universidade Pública, sempre estive envolvida em projetos de extensão e pesquisa, bolsista PIBIC e PIBEG, cresci profissionalmente procurando me especializar e ingressar no Mestrado. Especialista em UTI e em Saúde Pública, atualmente ocupo posição de gestão como Supervisora da Unidade de Neurocirurgia do Hospital de Base- DF, acompanhando uma equipe de quase 70 pessoas e cuidando em média de 50 pacientes, sou extremamente realizada profissionalmente e a minha carreira marca a minha vida com os melhores aprendizados.

A busca pelo Mestrado apenas se iniciou após me especializar e aprofundar no Sistema de Saúde brasileiro, sou apaixonada pelo SUS e, principalmente pelo que conseguimos fazer, mesmo diante de tantos desafios e dificuldades.

Na tentativa de iniciar o Mestrado me inscrevi por duas vezes no processo seletivo da ESCS, sem êxito na primeira tentativa, mas superando as expectativas na segunda oportunidade. Ao meu orientador que já possuía materiais importantes referente a temática, aceitei o desafio de escrever uma Revisão Sistemática e Metanálise em Rede, algo totalmente fora da minha zona de conforto. Aprendi a realizar uma excelente busca nas bases de dados, elaborar ótimos protocolos, interpretar gráficos e tabelas e a escrever de forma clara e concisa. Crescimento sem igual e muito desafiador.

Os resultados obtidos em nosso estudo são reais e válidos para uso diário nos nossos pacientes, colaborando com os profissionais de saúde para a decisão clínica e, sabendo que contribuí para a ciência, concluo esta etapa extremente realizada e grata por todo aprendizado e de coração aberto para novos projetos.

1. INTRODUÇÃO

A artrite reumatóide (AR) é uma doença inflamatória sistêmica, crônica e progressiva, que acomete primariamente a membrana sinovial das articulações, podendo levar à destruição óssea e cartilaginosa[1]. É considerada uma das doenças autoimunes mais comuns em todo o mundo[2]. No Brasil, a prevalência é de 0,2 a 1,0%, totalizando 400 mil a 2 milhões de pessoas acometidas pela AR[3]. O impacto da doença é devido ao aumento da incapacidade e a redução da qualidade de vida[4], que reflete em uma doença com custo considerável em termos de assistência médica e aspectos sociais[5].

O diagnóstico da AR é estabelecido considerando os achados clínicos e os exames complementares. Nenhum teste isolado, seja laboratorial, de imagem ou histopatológico, pode confirmar o diagnóstico[6].

Considerando tratar-se de uma doença autoimune, a artrite reumatóide não tem cura. Dessa forma, o objetivo do tratamento é controlar a inflamação, reduzir a dor, impedir a progressão da doença e o dano estrutural, preservar a capacidade funcional e melhorar a qualidade de vida dos indivíduos[7].

O tratamento farmacológico é considerado o ponto chave na terapêutica, e sua implantação precoce e intensiva previne danos estruturais, melhorando a capacidade funcional[8,9,11]. O período inicial da doença, principalmente os 12 primeiros meses, configura uma janela de oportunidade terapêutica, isto é, um momento em que a intervenção farmacológica efetiva pode mudar o curso da doença[9,11].

No Brasil, o Sistema Único de Saúde (SUS), por meio dos Componentes Básico (CBAF) e Especializado da Assistência Farmacêutica (CEAF), atualmente, disponibiliza para o tratamento medicamentoso de AR o uso de anti-inflamatórios não esteróides (AINE), glicocorticóides, medicamentos modificadores do curso da doença (MMCD) - sintéticos e biológicos - e imunossupressores.

De maneira geral, os MMCD biológicos reduzem a inflamação articular, o dano estrutural e a incapacidade funcional e melhoram a qualidade de vida e, possivelmente, a fadiga[12]. Os MMCD biológicos disponíveis no SUS são os anti-TNF (adalimumabe, certolizumabe pegol, etanercepte, golimumabe e infliximabe) e os não anti-TNF (abatacept, rituximab e tocilizumab).

No âmbito do CEAF, os medicamentos são dispensados mediante Protocolos Clínicos e Diretrizes Terapêuticas (PCDT), os quais estabelecem as estratégias de identificação e tratamento oportuno de AR, no contexto do SUS, com medicamentos eficazes, seguros e custo-efetivos para prevenir incapacidade e perda de qualidade de vida. O último Protocolo Clínico e Diretrizes Terapêuticas de Artrite Reumatóide foi publicado em 2019 pelo Ministério da Saúde, através da Comissão Nacional de Incorporação de Tecnologias – CONITEC.

Considerando a necessidade de disponibilizar esquemas terapêuticos de acordo com a melhor relação custo-minimização o MS publicou uma NOTA TÉCNICA Nº 411/2018-CGCEAF/DAF/SCTIE/MS no qual apresenta uma relaçao de medicamentos mais custo-efetivos para AR, entre eles escolhendo o Abatacept como medicação preferencial em pacientes com resposta terapêutica inadequada a agentes anti-TNF. Ainda que o protocolo se baseie exclusivamente no custo para a tomada de decisão, essa medida não caracteriza necessariamente uma estratégia de custo-efetividade, essencialmente porque não há uma demonstração definitiva de que existe equivalência entre os fármacos. Apesar de três meta-análises em rede sobre o tema sugerirem equivalência[13,14,15], a última delas de 2011, o poder estatístico dos estudos incluídos não era suficiente para afastar o risco de erro tipo II, ou seja, existe ainda elevada chance de resultado falso negativo. Desta forma, é fundamental uma nova avaliação dos estudos publicados e um novo estudo que avalie a combinação entre eficácia e segurança. Em paralelo, é importante entender a heterogeneidade entre os *trials* e encontrar maneiras de mitigá-la, de forma a permitir uma comparação adequada entre as drogas.

Neste sentido, o objetivo deste estudo é revisar sistematicamente a literatura, buscando avaliar os estudos clínicos randomizados a relação da eficácia e segurança entre rituximab, tocilizumab e abatacept em pacientes com AR refratários ao tratamento com MTX ou anti-TNF.

2. REVISÃO DE LITERATURA

2.1 CONCEITO E EPIDEMIOLOGIA

A artrite reumatoide (AR) é um distúrbio sistêmico, inflamatório, crônico, de

etiologia mal definida. O acometimento preferencial da doença envolve o sistema músculoesquelético em especial as articulações sinoviais, frequentemente conduz a um envolvimento articular grave, que determina dano estrutural, perda da função e limitações nas tarefas diárias dos pacientes[16]. O caráter crônico e destrutivo da doença pode levar a importante limitação funcional, com perda de capacidade laboral e de qualidade de vida, a menos que o diagnóstico seja feito em fase inicial da doença e o tratamento determine melhora clínica[17].Além de deformidade irreversível e de limitação funcional, pacientes com AR e doença avançada podem apresentar menor sobrevida, o que confirma a gravidade dessa doença[18,19.]

A incidência anual da doença é estimada em 0,2 casos por 1000 homens e 0,4 por 1000 mulheres. Em relação à prevalência, esta é aproximadamente similar em todo o mundo, atingindo cerca de 0,5 a 1% da população adulta[20,21].

Há poucos estudos de prevalência de AR na América Latina. No México, um estudo revelou a prevalência geral de 1,6%, com maior frequência entre as mulheres[22]. No Brasil, um estudo realizado em Minas Gerais encontrou prevalência de 0,46[23]. A AR é mais frequente em mulheres e na faixa etária de 30 a 50 anos, com pico de incidência na quinta década de vida[24]. Todavia, o histórico familiar de AR aumenta o risco de desenvolvimento da doença de 3 a 5 vezes[25].

As consequências negativas da doença, quando não adequadamente tratadas, podem ser extremamente prejudiciais para o indivíduo com perda funcional, incapacidade para o trabalho e redução acentuada na qualidade de vida. Para a saúde pública, a AR é responsável por altíssimos custos decorrentes do tratamento bem como da perda da produtividade dos pacientes acometidos pela doença[26,27,28].

2.2 DIAGNÓSTICO

Segundo as “Diretrizes para o diagnóstico da artrite reumatoide” o diagnóstico é estabelecido considerando-se achados clínicos e exames complementares. Entre eles, considerar o tempo de evolução da artrite, a presença de autoanticorpos (quando disponível a sua determinação), a elevação de provas de atividade inflamatória e as alterações compatíveis em exames de imagem. Nenhum teste isolado, seja laboratorial, de imagem ou histopatológico, é capaz de confirmar o diagnóstico[29].

Alguns critérios de classificação como American College of Rheumatology - ACR 1987 e ACR/European League Against Rheumatism - ACR/EULAR 2010 auxiliam no processo diagnóstico e são adotados por pesquisadores para a identificação e inclusão de indivíduos com determinada doença em estudos clínicos. Por outro lado, critérios de diagnóstico têm como objetivo auxiliar o especialista a identificar esses indivíduos na prática clínica diária[30].

Em 2010, o American College of Rheumatology e a European League Against Rheumatism revisaram e atualizaram os critérios classificatórios propostos pelo American College of Rheumatology, em 1987[31]. Os critérios atualizados (Quadro 1) se baseiam em um sistema de pontuação por meio de um escore de soma direta. As manifestações são divididas em quatro domínios: acometimento articular, sorologia, duração dos sintomas e provas de atividade inflamatória. Em caso de dúvida, a contagem de articulações acometidas pode usar métodos de imagem (ultrassonografia ou ressonância magnética). Uma pontuação maior ou igual a seis conclui pelo diagnóstico[29].

Quadro 1 - Critérios do American College of Rheumatology/European League Against Rheumatism (2010) para classificação de indivíduos com artrite reumatóide.

Critérios	Pontuação
Envolvimento articular[1]	**0 a 5 pontos** - 1 grande articulação: 0 - 2 a 10 grandes articulações: 1 - 1 a 3 pequenas articulações (grandes não contabilizadas): 2 - 4 a 10 pequenas articulações (grandes não contabilizadas): 3 - mais de 10 articulações (ao menos uma pequena articulação): 5
Sorologia[2]	**0 a 3 pontos** - FR e anti-CCP negativos: 0 - FR ou anti-CCP positivos em baixos títulos: 2 - FR ou anti-CCP positivos em altos títulos: 3
Duração dos sintomas[3]	**0 a 1 ponto** - Inferior a 6 semanas: 0 - Igual ou superior a 6 semanas: 1
Provas de atividade inflamatória[4]	**0 a 1 ponto** - PCR e VHS normais: 0 - PCR ou VHS alterada: 1

Fonte: Aletaha et al. (2010), Mota et al. (2013) e Brasil (2015a).
Legenda: Anti-CCP - Anticorpo contra peptídeo citrulinado cíclico; FR – Fator reumatoide; IFDs - Interfalangeanas distais; IFPs - Interfalangeanas proximais; MCFs – Metacarpofalangeanas; MTF – Metatarsofalangeanas; PCR – Proteína C reativa; VHS - Velocidade de hemossedimentação.

Notas: 1 - Qualquer articulação dolorosa ou edemaciada, excluindo articulações IFDs de mãos e pés, primeira MTF e primeira carpometacárpica. Considera-se, para fins de classificação: pequenas articulações - MCFs, IFPs, MTF (segunda a quinta), primeira interfalangeana e punhos; grandes articulações - ombros, cotovelos, quadril, joelhos, tornozelos. Articulações adicionais (temporomandibular, esternoclavicular, acromioclavicular, entre outras) podem ser contabilizadas na avaliação de "mais de 10 articulações", desde que ao menos uma pequena articulação esteja acometida.
2 - Considera-se resultado: negativo - valor inferior ou igual ao limite superior de normalidade; baixos títulos – valor maior que o limite superior da normalidade, mas inferior ou igual até três vezes esse limite; altos títulos – valor maior que três vezes o limite superior da normalidade.
3 - Relato do próprio indivíduo.
4 - Consideradas normais ou anormais, conforme o valor de referência dos métodos adotados

Os critérios de 2010 têm por objetivo classificar pacientes com manifestações recentes da doença. Pacientes com doença erosiva típica de AR e história compatível com preenchimento prévio dos critérios de 2010 devem ser classificados como tendo AR. Pacientes com doença de longa duração, mesmo com doença inativa (com ou sem tratamento), com base em dados retrospectivos e que preencheriam os critérios de 2010 devem ser classificados com tendo AR[32].

Segundo Mota (2013), o diagnóstico clínico é extremamente complexo, e inclui inúmeros aspectos que, dificilmente, poderiam ser expressados na forma de um escore de critérios. Eventualmente, esses critérios podem servir como um guia para o estabelecimento do diagnóstico clínico.

A AR é uma doença heterogénea, uma vez que pacientes que preencham os critérios de classificação do ACR podem ter uma evolução clínica auto-limitada ou uma doença severa e progressiva[33].

Do ponto de vista prognóstico, são referidos pelas recomendações da EULAR - European League Against Rheumatism para a abordagem da artrite precoce, alguns factores que se associam a uma pior evolução, tais como: número de articulações dolorosas e tumefactas, valor da VS e PCR, título do Factor Reumatóide (FR) e do Anticorpo Anti-péptido Citrulinado Cíclico (Anti-CCP) e evidência radiográfica de erosões[34]. Outros factores predictores de mau prognóstico incluem tabagismo e baixo nível sócio-económico[35].

Entre os exames complementares que auxiliam no diagnóstico da artrite reumatoide, destacam-se os laboratoriais(provas de atividade inflamatória, fator reumatoide, anti-CCP, outros autoanticorpos e avaliação genética) e os de imagem (radiografia convencional, ultrassonografia e ressonância magnética[29].

2.3 TRATAMENTO

Considerando tratar-se de uma doença autoimune, a artrite reumatoide não tem cura. Dessa forma, o objetivo do tratamento é controlar a inflamação, reduzir a dor, impedir a progressão da doença e o dano estrutural, preservar a capacidade funcional e melhorar a qualidade de vida dos indivíduos[7].

O tratamento da AR é considerado bastante dinâmico, o mesmo irá variar de acordo com a intensidade da doença, sendo assim necessário uma reavaliação constante. Segundo o estudo de Chechi et al, (2014), os tratamentos existentes podem ser farmacológicos e não farmacológicos[36].

2.3.1 TRATAMENTO NÃO FARMACOLÓGICO

Segundo o "Consenso da Sociedade Brasileira de Reumatologia para o Tratamento da Artrite Reumatoide" (2012), as atividades educativas são essenciais para que se obtenha a colaboração do indivíduo e da família. O indivíduo precisa participar ativamente das escolhas realizadas e, para isso, precisa conhecer sua condição clínica e as opções terapêuticas disponíveis. O indivíduo que compreende sua condição, a ação e importância dos medicamentos, os métodos de prevenção de deformidades e o processo de reabilitação apresenta melhor evolução clínica[37].

O tratamento não medicamentoso de AR inclui educação do paciente e de sua família, terapia ocupacional, exercícios, fisioterapia, apoio psicossocial e cirurgia. As evidências de tratamento não medicamentoso são escassas, mas acredita-se que tenha papel importante na melhora clínica e funcional dos pacientes[38-46].

Exercícios contra resistência são seguros e eficazes na AR, melhorando a força muscular e o tempo de deslocamento[47,48]. Exercícios aeróbicos parecem melhorar de forma discreta a qualidade de vida, a capacidade funcional e a dor em pacientes com AR estável[49-53].

Em síntese, aos indivíduos com artrite reumatoide, incluindo casos especiais, é recomendado exercício físico regular, terapia ocupacional, órteses, fisioterapia e terapia psicológica individualizada[30].

2.3.2 TRATAMENTO FARMACOLÓGICO

O tratamento medicamentoso de AR inclui o uso de anti-inflamatórios não esteroidais (AINE), glicocorticoides, medicamentos modificadores do curso da doença (MMCD) - sintéticos e biológicos - e imunossupressores[37,54].

O Ministério da Saude elaborou uma atualização do Protocolo Clínico e Diretrizes Terapêuticas Artrite Reumatóide para tratamento da AR no Brasil em 2019, na qual constam princípios gerais, e o fluxograma com os esquemas terapêuticos recomendados.

O uso da metaterapêutica (*treat to target*) é recomendado em pacientes com AR, independentemente do nível de atividade da doença. O princípio do tratamento por meta terapêutica é estabelecer uma meta para o controle dos sintomas, levando em consideração a decisão compartilhada entre o paciente e o profissional da saúde, podendo ser repactuada ao longo do seguimento. O paciente deve expressar suas preferências (por exemplo: vias de administração, intervalos de aplicação e efeitos adversos) para garantir sua aderência. Deve-se observar sempre o balanço entre custos e benefícios, facilidade de acesso, disponibilidade de medicamentos, condições de armazenamento, existência de centros de infusão e educação do paciente[32].

O Sistema Único de Saúde (SUS) disponibiliza como recursos medicamentosos para o tratamento da AR os MMCD, ou seja, fármacos que previnem o dano e preservam a integridade e funcionalidade articular. Estes tratamentos são disponibilizados pelo Componente Especializado da Assistência Farmacêutica (CEAF)[55].

Os medicamentos disponibilizados para o tratamento da Artrite reumatoide no âmbito do SUS são:

Anti-inflamatórios não esteroidais (AINE)	• ibuprofeno: comprimidos de 200, 300 e 600 mg; suspensão oral de 50 mg/mL. • naproxeno: comprimidos de 250 mg e 500 mg.
Glicocorticoides	• metilprednisolona pó para solução injetável 500mg • prednisona: comprimidos de 5 e 20 mg. • fosfato sódico de prednisolona: solução oral de 1 e 3 mg/mL.

Medicamentos modificadores do curso da doença - sintéticos	• metotrexato: comprimidos de 2,5 mg; solução injetável (frasco com 2mL) • 25mg/ml. • sulfassalazina: comprimidos de 500 mg. • leflunomida: comprimidos de 20 mg. • sulfato de hidroxicloroquina: comprimidos de 400 mg. • difosfato de cloroquina: comprimidos 150 mg
Medicamentos modificadores do curso da doença - imunobiológicos	• adalimumabe: solução injetável 40 mg. • certolizumabe pegol: solução injetável 200 mg. • etanercepte: solução injetável 25 e 50 mg. • infliximabe: pó para solução injetável 100 mg/10mL. • golimumabe: solução injetável 50 mg. • abatacept: pó para solução injetável 250mg e solução injetável 125 mg/mL. • rituximab: solução injetável (frasco com 50mL) 10mg/mL. • tocilizumab: solução injetável (frasco com 4mL) 20mg/mL.
Medicamentos modificadores do curso da doença - Inibidores da JAK	• tofacitinibe: comprimidos de 5 mg.
Imunossupressores	• ciclosporina: cápsulas de 10, 25, 50 e 100 mg; solução oral de 100 mg/mL em frascos de 50 ml. • ciclofosfamida: comprimidos de 50 mg. • azatioprina: comprimidos de 50 mg

Fonte: Ministério da Saúde, 2019.

A AR possui um período de intervenção terapêutica de 12 meses, sendo que neste período deve-se implementar o tratamento farmacológico de forma rápida e efetiva para poder ter a oportunidade de mudar a realidade da doença, ou seja o seu curso[37].

De acordo com o Protocolo Clínico e Diretrizes Terapêuticas Artrite Reumatóide do Ministério da Saúde, 2019 as seguintes etapas e linhas terapêuticas são preconizadas para o tratamento medicamentoso da artrite reumatóide:

- **PRIMEIRA ETAPA**

MEDICAMENTOS MODIFICADORES DO CURSO DA DOENÇA SINTÉTICOS (MMCDs): Metotrexato, leflunomida, sulfassalazina e hidroxicloroquina.

1ª LINHA

O metotrexato (MTX) deve ser a primeira escolha terapêutica. Na impossibilidade de uso do MTX por toxicidade, deve-se usar, preferencialmente, a leflunomida (LEF) ou sulfassalazina (SSZ), sendo a terapia isolada com hidroxicloroquina (HCQ) pouco efetiva. O MTX está associado a alta taxa de toxicidade hepática e gastrointestinal, podendo levar à suspensão do tratamento em aproximadamente 30% dos casos[32].

2ª LINHA

Em caso de falha da monoterapia inicial (MTX, LEF ou SSZ), isto é, de persistência da atividade de doença (de acordo com a meta terapêutica) após 3 meses de tratamento otimizado (dose máxima tolerada e adesão adequada) do medicamento usado na 1ª linha, passa-se para a terapia com a combinação dupla ou tripla de MMCDs. As associações mais comumente recomendadas são MTX ou LEF com HCQ ou SSZ[32].

- **SEGUNDA ETAPA**

MEDICAMENTOS MODIFICADORES DO CURSO DA DOENÇA BIOLÓGICOS (MMCDbio): Abatacept, adalimumabe, certolizumabe pegol, etanercepte, golimumabe, infliximabe, rituximab, tocilizumab – e tofacitinibe.

Após o uso de pelo menos dois esquemas terapêuticos na primeira etapa por no mínimo 3 meses cada um e havendo persistência da atividade da doença conforme um CDAI, utiliza-se um MMCDbio ou do tofacitinibe. O MMCDbio deve ser usado em associação com o MTX, exceto no caso de contraindicação; neste caso, pode ser considerada a associação com outro MMCDs (LEF e SSZ).

Os MMCDbio que podem ser usados são os anti-TNF (certolizumabe,pegol, golimumabe, infliximabe, etanercepte e adalimumabe) e os não anti-TNF (abatacept e tocilizumab). O uso do rituximab deve ser reservado somente aos indivíduos com contraindicação absoluta a todos os MMCDbio anti-TNF e também ao abatacept e tocilizumab[32].

- **TERCEIRA ETAPA**

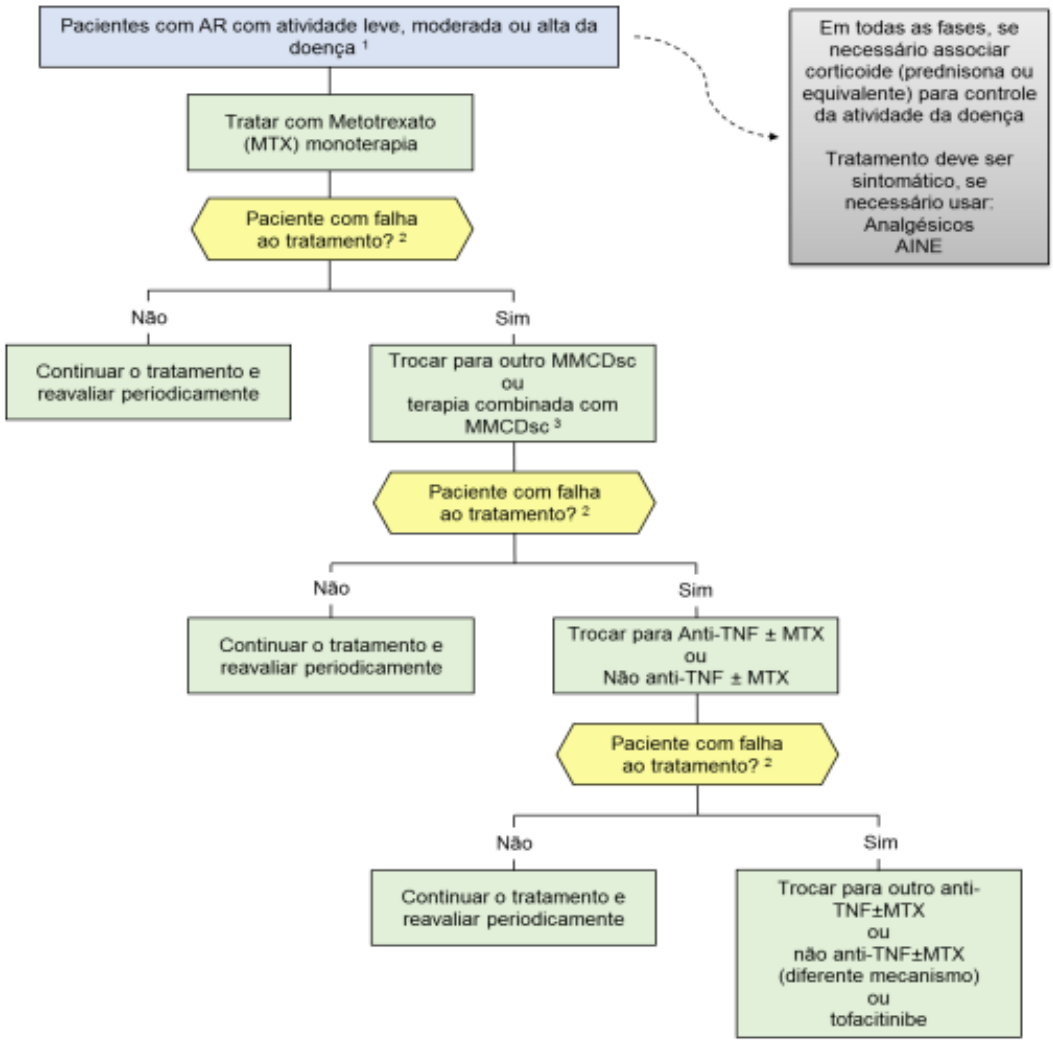
MEDICAMENTOS MODIFICADORES DO CURSO DA DOENÇA BIOLÓGICOS (MMCDbio) - Abatacept, adalimumabe, certolizumabe pegol, etanercepte, golimumabe, infliximabe, rituximab, tocilizumab – e tofacitinibe.

Após pelo menos 3 meses da segunda etapa terapêutica, e havendo persistência da atividade da doença conforme um CDAI, ou toxicidade inaceitável ao medicamento utilizado nessa etapa, pode-se prescrever outro MMCDbio (anti-TNF ou não anti-TNF) ou o tofacitinibe, desde que o medicamento selecionado não tenha sido usado anteriormente. Se possível, o medicamento selecionado deve ser associado a um MMCD (preferencialmente o MTX).

Em qualquer das etapas discriminadas anteriormente, podem ser utilizados AINE e glicocorticoides para controle sintomático, na menor dose e pelo menor tempo possível[32].

No Brasil, o tratamento da AR pode ser visualizada na Figura 1, que mostra o fluxo de tratamento medicamentoso da diretriz do Ministério da Saúde (MS) para o tratamento da AR descrito no Protocolo Clínico e Diretrizes Terapêuticas (PCDT/MS).

Figura 1. Fluxograma de tratamento do PCDT do MS do Brasil



1.Tratamento com meta terapêutica: remissão ou baixa atividade da doença (reavaliar periodicamente)
2. A falha ao tratamento pode se dar por eventos adversos ou ausência de eficácia (não atingimento de meta terapêutica). Para avaliar
eficácia deve aguardar pelo menos 3 meses de tratamento com esquema vigente, não devendo ser trocada de linha terapêutica em intervalo de tempo inferior.
3.Considerar substituição do uso de MTX injetável ou outras combinações de terapias duplas ou triplas. Considerar MTX injetável,Leflunomida, terapia dupla ou tripla, sem MTX oral.

O objetivo do tratamento geralmente é a remissão da atividade da doença, sendo aceitável a baixa atividade em casos específicos. Neste caso, a atividade da AR pode ser medida por meio de índices combinados de atividade de doença (CDAI) e algum instrumento de medida da capacidade funcional, como o Health Assessment Questionnaire (HAQ)[32].

Em qualquer das linhas discriminadas para o tratamento dos pacientes com AR, glicocorticoides e/ou AINEs podem ser prescritos para controle sintomático, optando-se pelo uso da menor dose pelo menor tempo possível. Os AINEs disponíveis

no SUS são o ibuprofeno e naproxeno. O uso crônico desses medicamentos indica que a atividade da AR não está adequadamente controlada com os MMCDsc e/ou MMCDbio, devendo o tratamento ser revisto. Esses medicamentos estão associados a sintomas do trato gastrointestinal, incluindo náuseas, gastrite, dispepsia, podendo ocorrer hemorragia digestiva com seu uso prolongado. Seu uso deve ser reservado para alivio sintomático enquanto espera-se efeitos dos MMCDsc e/ou MMCDbio.

Idealmente o tratamento do paciente com AR deve ser multidisciplinar, incluindo promoção da saúde, controle de comorbidades e imunizações. Importante instruir e verificar com o paciente as condições de armazenamento e de administração dos medicamentos, em especial naqueles em uso de MMCDbio, os quais requerem refrigeração e uso parenteral. Mesmo os pacientes inseridos em serviços de atenção especializada devem realizar acompanhamento na APS, sendo esta co-responsável pelo seu manejo[32].

2.4 MEDICAMENTOS MODIFICADORES DO CURSO DA DOENÇA – BIOLÓGICOS

Os medicamentos modificadores do curso da doença sejam sintéticos ou biológicos são comprovados como efetivos para a modificação do curso da doença, segundo estudos de Faleiro, (2010), o mesmo age diretamente no tratamento dos sintomas mais severos da AR[56].

Entre os medicamentos incluídos no Protocolo Clínico e Diretrizes Terapêuticas da Artrite Reumatoide do Ministerio da Saúde (2019) e aprovados pela Anvisa destacam-se:

Abatacept

O abatacept é um fármaco antirreumático modificador da AR ativa, moderada a grave, em pacientes adultos com resposta inadequada a MMCD ou aos anti-TNF, podendo ser usado em associação com MMCD ou em monoterapia[57]. Abatacept é uma proteína de fusão, um modulador seletivo da coestimulação, que inibe a ativação de linfócitos T, processo que ocorre no início da reação inflamatória. Desta forma, impede a cadeia de eventos que leva à inflamação das articulações, prevenindo a dor e o dano articular. Ele é administrado por via intravenosa durante aproximadamente 30 minutos e, subsequente a primeira dose, são aplicadas doses adicionais em duas

e quatro semanas e depois a cada quatro semanas.[58] No Brasil, o produto foi registrado pela ANVISA apenas em 2010[59].

Basicamente, o abatacept liga-se ao CD80 e ao CD86 nas células apresentadoras de antígeno, impedindo que estas moléculas se liguem ao CD28 nas células T e, assim, inibindo a ativação ótima das células T, bloqueando o sinal co-estimulatório. Dessa forma, a modulação seletiva da co-estimulação representa uma abordagem terapêutica racional em pacientes com uma resposta inadequada ao anti-TNF- terapia α[60].

Rituximab

Rituximab é um fármaco antineoplásico e antirreumático e que se liga a receptores nos linfócitos B, levando à destruição dessas células de 3 a 4 meses após a última infusão. Os pacientes com fator reumático (FR) ou anti-CCP parecem apresentar melhor resposta ao tratamento com este fármaco. Reações infusionais, em geral leves, podem ocorrer em até 35% dos casos na primeira administração e em cerca de 10% na segunda. Infecções, pneumonia intersticial, neutropenia e trombocitopenia podem ser complicações do tratamento com rituximab. Recomendado na AR ativa moderada a grave, em pacientes adultos, com resposta inadequada ou intolerância a um ou mais anti-TNF, devendo ser usado em associação com metotrexato[61].

Tocilizumab

Tocilizumab é um fármaco antirreumático modificador da doença, utilizado na AR ativa moderada a grave, em pacientes adultos, com resposta inadequada a MMCD ou antiTNF, pode ser usado em associação com MMCD ou em monoterapia. A curto prazo, reduz a atividade de doença e melhora a capacidade funcional do doente, havendo, no entanto, evidências de aumento significativo nos níveis de colesterol em estudos iniciais[62].

Sendo um anticorpo monoclonal humanizado anti-receptor da IL-6 humana (IL-6R), o tocilizumab inibe as atividades biológicas da IL-6. O tratamento de pacientes com artrite reumatoide (AR) com tocilizumab causa uma redução significativa na atividade da doença, porém, ainda não está claro por que a inibição da IL-6 produz essa melhora. Acredita-se que as células inflamatórias desempenhem papéis cruciais no desenvolvimento e manutenção da sinovite. Portanto, é possível que melhorias no

inchaço das articulações após o tratamento com tocilizumab possam ser devidas a uma redução no número de células inflamatórias nas articulações[63].

3. OBJETIVO

3.1 Geral

- Avaliar eficácia entre rituximab, tocilizumab e abatacept em pacientes com AR refratários ao tratamento com MTX ou anti-TNF.

3.2 Especificos

- Revisar sistematicamente a literatura, através de estudos clínicos randomizados e comparar indiretamente os tratamentos para AR entre rituximab, tocilizumab e abatacept;
- Avaliar o impacto dos tratamentos para AR com rituximab, tocilizumab e abatacept sobre a resposta ACR;

4. METODOLOGIA

4.1 Desenho do estudo

Para a realização deste estudo, foi realizada uma revisão sistemática com metanálise em rede para investigar o controle de atividade da doença em pacientes com AR em ensaios clínicos randomizados com rituximab, tocilizumab ou abatacept. Em seguida, com a apropriação dos resultados da revisão sistemática e da metanálise em rede, foi realizada uma análise de meta-regressão, avaliando a sensibilidade e heterogenidade das covariáveis.

A revisão foi registrada na base International Prospective Register of Systematic Reviews do Centre for Reviews and Dissemination / University of York (PROSPERO). Número do registro: CRD42020167953 (Apêndice A). O protocolo de estudo seguiu as normas do PRISMA(Apêndice B)[64.]

4.2 Critérios de elegibilidade

Para a pesquisa foram incluídos estudos clínicos (RCTs) mostrando pacientes

com artrite reumatóide refratária ao tratamento com agentes anti-TNF, randomizados para tratamento com Rituximab, Abatacept ou Tocilizumab (grupo ativo) ou para tratamento com placebo com metotrexato ou drogas anti-TNF (grupo de controle) com avaliação de eficácia.

Foram excluídos artigos de revisão de literatura, editoriais, registros de conferências, resumos ou anais de congressos, estudos *in vitro* e que consideraram modelos em animais, estudos qualitativos, estudos transversais, estudos de caso-controle, revisões sistemáticas, estudos que evidenciaram tratamentos alternativos com antibióticos, estudos com tempo de exposição inferior a 24 semanas, pesquisas que consideraram pacientes com outros tipos de doenças autoimunes, investigações do uso de tocilizumab, rituxumabe ou abatacept para tratamento de outras doenças, pesquisas que incluíram pacientes com comorbidades: grávidas, lactantes, histoplasmose, coccidiomicose, HIV, tuberculose etc, e análises de pacientes com hipersensibilidade ao rituximab ou abatacept ou tocilizumab.

4.3 Estratégia de busca

As bases de dados MedLine (PubMed), Cochrane Library, Embase, Web of Science, Scopus, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e literatura cinzenta (Opengrey e Google acadêmico); foram pesquisadas para artigos originais, até a data de 18 de julho de 2020, na busca de identificar todos os RCTs que avaliem a relação entre eficácia e segurança de rituximab, tocilizumab e abatacept em pacientes com AR refratários ao tratamento com MTX ou drogas anti-TNF.

Na busca foram empregados descritores identificados previamente no DeCS (Descritores em Ciências da Saúde, http://decs.bvs.br/), no Mesh (Medical SubjectHeadings, https://www.nlm.nih.gov/mesh/meshhome.html) e no Emtree Terms https://www.embase.com, bem como seus respectivos sinônimos, com o intuito de incluir a maior quantidade de estudos relevantes.

A estratégia de busca utilizada está detalhada na Tabela S1 do Material Suplementar. Os termos das pesquisas foram procurados em títulos, palavras-chaves e resumos.

4.4 Seleção dos estudos e extração dos dados

A primeira seleção de artigos foi realizada a partir da leitura dos títulos, e a segunda seleção a partir da análise dos resumos e palavras-chave. Para gerenciar os arquivos duplicados foi utilizado o aplicativo *Rayyan QCRI*, um sistema da web e móvel gerenciador de referências para revisões sistemáticas. Os títulos e resumos de todos os artigos identificados pela estratégia de busca foram avaliados por dois dos autores deste trabalho, de forma independente.

Na segunda fase os revisores avaliaram independentemente os artigos completos e fizeram suas seleções, de acordo com os critérios de elegibilidade pré-especificados. Foram avaliados desfechos primários e secundários. O primário foi: a taxa de resposta ACR70 de acordo com os critérios do *American College of Rheumatology* (pelo menos 70% de melhora no número de articulações inchadas e doloridas, e em três dos cinco parâmetros: avaliação global do médico da doença, paciente global avaliação da doença, avaliação do paciente quanto à dor, proteína C reativa ou taxa de sedimentação de eritrócitos e o Questionário de Avaliação da Saúde (pontuação HAQ) em 24–30 semanas. A resposta ACR70 foi escolhida como desfecho primário por sua elevada especificidade em relação a melhora de funcionalidade e qualidade de vida.

Os defechos secundários foram: critérios de resposta ACR 50 e ACR20, sendo comparadas entre tratamentos para identificar diferenças no padrão de resposta do ACR.

Os dados extraídos dos estudos foram inseridos e organizados em uma planilha Microsoft Excel®. Após a padronização das informaçoes, os dados foram exportados para outro sistema informatizado (pacote “gemtc” para R) para análise estatística.

4.5 Qualidade metodológica e risco de viés

A avaliação da qualidade metodológica e do risco de viés foi realizada de maneira independente por dois revisores e as discordâncias foram resolvidas por consenso. A qualidade dos estudos foi avaliada com o “*Grading of Recommendations Assessment, Development and Evaluation* – GRADE.[65] Já o risco de viés foi avaliado por meio da ferramenta da Cochrane Collaboration (*Risk of bias in randomized trials*

– *RoB 2*), que considera seis dimensões: geração da sequência aleatória, sigilo da alocação, cegamento de participantes e profissionais, cegamento de avaliadores de desfecho, dados de desfechos incompletos e relato de desfecho seletivo.[66]

5. ANÁLISE ESTATÍSTICA

Foi utilizado o modelo de efeitos aleatórios para a meta-análise da rede Bayesiana[67]. Utilizamos média e desvio padrão para representar variáveis dentro dos RCTs. Todos os resultados foram expressos como *hazard ratios* (HRs) e os seus correspondentes intervalos de confiança de 95% (IC). A análise foi feita utilizando os métodos da cadeia de Markov Monte Carlo. Três cadeias foram adequadas, produzindo 5.000 interações (20.000 por cadeia) gerando as distribuições posteriores dos parâmetros do modelo. O diagnóstico de convergência foi feito utilizando o teste Brooks-Gelman-Rubin[68]. O ajuste do modelo foi avaliado através do cálculo do desvio residual. A estatística I^2 foi utilizada para investigar as possibilidades de heterogeneidade estatística e criamos um gráfico de funil ajustado por comparação para detectar a presença de qualquer viés de publicação[69]. Para avaliar a inconsistência, realizamos a abordagem de "divisão de nós"[69]. Para explorar a associação entre log-HR para alcançar a resposta ACR70, realizamos uma análise de metaregressão, em que os efeitos de tratamento relativos ao abatacept dependeram do seguimento do estudo, da presença de terapias anti-TNF no braço controle e da pontuação média de base do Questionário de Avaliação da Saúde (HAQ)[67]. A análise de sensibilidade foi realizada excluindo os ensaios que calcularam as maiores exposições (indivíduos tratados por ano- paciente/ano) por classe de fármacos. As análises estatísticas foram conduzidas com o *software R* Studio versão 1.1.4 (R versão 4.0.1 como linguagem de programação - *R Foundation for Statistical Computing*, Auckland, NZ).

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Article: Compared efficacy of rituximab, abatacept, and tocilizumab in patients with rheumatoid arthritis refractory to methotrexate or anti-TNF agents: a systematic review and network meta-analysis

ABSTRACT

Background: Although disease-modifying antirheumatic drugs (DMARD), including synthetic ones, such as methotrexate (MTX), and biological ones (bDMARD), such as tumor necrosis-factor inhibitors (anti-TNF agents), have unquestionably improved the quality of life of individuals with rheumatoid arthritis (RA), at least one third of individuals do not respond to these treatments. Rituximab, abatacept, and tocilizumab are bDMARD options available, but it is unclear whether any of these drugs is superior to the others.

Objective: To compare the efficacy of rituximab, tocilizumab, and abatacept in individuals with RA refractory to treatments with MTX or anti-TNF agents.

Data sources: PubMed, Cochrane Library, Embase, Web of Science, Scopus, and LILACS until July 18, 2020.

Study selection: Phase 2-4 randomized controlled trials (RCTs) evaluating patients with RA refractory to MTX or anti-TNF therapy treated with rituximab, abatacept, and tocilizumab (intervention arm) compared to controls.

Data extraction: Study characteristics, quality, and data were independently assessed by two investigators. The primary outcome was a 70% reduction in disease activity according to the American College of Rheumatology response criteria (ACR70).

Data synthesis: The meta-analysis included 19 RCTs, with 7,835 patients randomized to the intervention vs. control arms and a mean study duration of 1.2 years. The mean age was 52.3 years, 77.2% of individuals were women, and the mean disease duration was 8.7 years. The hazard ratios (HRs) for achieving an ACR70 response at six months were not different among the bDMARDs when compared to placebo, however,

there was a high heterogeneity. Three factors showing a critical imbalance among the bDMARD classes were identified: baseline HAQ score, study duration, and frequency of anti-TNF treatment in the control arm. To better understand the heterogeneity among RCTs, multivariate meta-regression adjusted to these three factors were conducted for the relative risk (RR) for achieving an ACR70 response during the study follow-up. Thus, heterogeneity was attenuated (I^2 = 24%, p for heterogeneity = 0.27) and the explanatory power of the model increased (R^2 = 85%). In this model, rituximab did not modify the chance of achieving an ACR70 response compared to abatacept (RR = 1.773, 95% CI 0.113–10.21, p = 0.765). In contrast, abatacept was associated with a RR = 2.217 (95% CI 1.554–3.161, p < 0.001) for ACR70 compared to tocilizumab.

Conclusion: In the network meta-analysis, there was no significant difference among tocilizumab, abatacept, and rituximab in achieving an ACR70 response, there being a low inconsistency, but high heterogeneity among studies. Based on the result of multivariate meta-regressions, if the conditions of the RCTs were similar, we estimate that abatacept could increase the chance of reaching an ACR70 response by 2.2-fold compared to tocilizumab.

Keywords: Rheumatoid arthritis; Rituximab; Abatacept; Tocilizumab; bDMARD; American College of Rheumatology; Network meta-analysis; Meta-regression.

Abbreviations:

ABA, abatacept; ACR, American College of Rheumatology; bNMA, Bayesian network meta-analysis; Cis, confidence intervals; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HAQ, Health Assessment Questionnaire; HRs, hazard ratios; LILACS, Latin American and Caribbean Literature in Health

Sciences; MTX, methotrexate; PRISMA, Preferred reporting items for Systematic Reviews and Meta- Analyses; PROSPERO, Prospective Register of Systematic Reviews; RA, Rheumatoid Arthritis; RCTs, randomized clinical trials; RR, relative risk; RTX, rituximab; TCZ, tocilizumab; TNF, tumor necrosis factor.

1. INTRODUCTION

Successive paradigm shifts have marked the treatment of rheumatoid arthritis (RA) in the past two decades. Following the changing environment, clinical discussion around the choice of immunobiologicals is increasingly complex. Traditionally used as a first-line treatment after methotrexate (MTX) failure, therapy with tumor necrosis factor inhibitors (anti-TNF agents) improves the quality of life of most individuals with RA. However, at least one third of individuals do not respond to these agents [1,2].

Treatments with rituximab (RTX, a B lymphocyte depleting agent), abatacept (ABA, a T cell co-stimulation modulator), and tocilizumab (TCZ, an interleukin-6 receptor inhibitor) are available options [3-5]. These three drugs have demonstrated good efficacy compared to placebo, and similar or greater efficacy vs adalimumab in head-to-head clinical trials (reference AMPLE and ADACTA trial), however, there are no head-to-head studies comparing efficacy between them. Such comparisons, unfortunately, will probably never be carried out. In these scenarios, network meta-analysis could allow an approach to shed light on this uncertain data.

There are three network meta-analyses [6-8] available comparing drugs used in the treatment of patients with RA refractory to anti-TNF or MTX therapies. Despite pointing to a similar effectiveness among drugs, it is important to highlight that few data were available at the time of publication of these studies, with their low statistical power suggesting a risk of type II error greater than 30%. Other meta-analyses of randomized

or observational studies [9,10] presented a low quality and/or highly heterogeneous data. The essential problem with not having a conclusive study demonstrating an equivalence among drugs is that public policies based on cost minimization can be arbitrarily implemented.

Therefore, a new assessment of published studies and a new study analyzing the combination of the efficacy and safety of such drugs are essential. It is also important to understand the existing heterogeneity among trials, finding ways to mitigate it to allow an adequate comparison among treatments.

In this sense, the aim of this study is to systematically review the literature seeking to evaluate randomized clinical trials (RCTs) on the efficacy and safety of RTX, TCZ, and ABA in individuals with RA refractory to MTX or anti-TNF therapies.

2. METHODS

2.1 Study design

This systematic review used a network meta-analysis to investigate efficacy of RTX, TCZ or ABA in patients with RA in RCTs. Then, with the results obtained from the systematic review and network meta-analysis, meta-regression analyses were performed to evaluate the sensitivity and heterogeneity among trials and the influence of covariates.

The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) of the Centre for Reviews and Dissemination at the University of York under number CRD42020167953. The study protocol followed the rules of PRISMA [11].

2.2 Eligibility criteria

Inclusion criteria were restricted to RCTs designed to evaluate the disease severity in individuals with RA refractory to treatment with anti-TNF agents or MTX. All RCTs should assess the efficacy of treatments and include a RTX, ABA, or TCZ intervention arm and a placebo arm treated with or without MTX and/or anti-TNF agents (control arm).

We excluded literature reviews, editorials, conference records, congress annals or abstracts, in vitro and animal model studies, qualitative studies, cross-sectional studies, case-control studies, systematic reviews, studies that evidenced alternative treatments using antibiotics, studies with an exposure time of less than 24 weeks, researches that considered patients with other types of autoimmune diseases, investigations of the use of TCZ, RTX, or ABA to treat other diseases, studies that included patients with comorbidities (pregnancy, breastfeeding, histoplasmosis, coccidioidomycosis, HIV, tuberculosis etc.), and analyses of individuals with hypersensitivity to RTX, ABA, or TCZ.

2.3 Search strategy

To identify all RCTs that assess the relationship between the efficacy and safety of RTX, TCZ, and ABA in individuals with RA refractory to treatment with anti-TNF agents or MTX, searches for original articles were conducted in the MedLine (PubMed), Cochrane Library, Embase, Web of Science, Scopus, and Latin American and Caribbean Literature in Health Sciences (LILACS) databases until July 18, 2020.

The search strategy used is detailed in the **Supplementary Table A.** The term search was focused on titles, keywords, and abstracts.

2.4 Study selection and data extraction

The first study selection stage consisted of reading the titles, further encompassing abstracts and keywords in a second step. The Rayyan QCRI application (Rayyan Systems Inc., 1 Broadway, 14th Floor Cambridge, Massachusetts, EUA), a web and mobile reference manager for systematic reviews, was used to manage duplicate files. The titles and abstracts of all articles identified by the search strategy were independently assessed by two authors of the present study.

In the second stage, the investigators independently evaluated the full text of the articles and made their selections according to the pre-specified eligibility criteria. Primary and secondary outcomes were assessed. The primary outcome was an ACR70 response according to the American College of Rheumatology (ACR) criteria, i.e., at least 70% improvement in the number of swollen and painful joints and improvement in three of these five parameters: physician's global assessment of the disease, patient's global assessment of the disease, patient's assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and Health Assessment Questionnaire (HAQ) score. The ACR score measures the rheumatic disease activity and is used to measure differences in relation to the baseline, showing a good relationship with the quality of life and functionality [12]. The ACR20, ACR50, and ACR70 responses refer to an improvement of 20%, 50%, and 70% in the ACR score, respectively.

The ACR70 response was chosen as the primary outcome due to its high specificity in relation to the functionality and quality of life improvement [13]. The secondary outcomes were the ACR50 and ACR20 response criteria compared among treatments to identify differences in the ACR response pattern.

Data extracted from studies were inserted, organized, and standardized in a Microsoft Excel® (Microsoft Corporation, One Microsoft Way Redmond, Washington, EUA) spreadsheet.

2.5 Methodological quality and risk of bias

The methodological quality and risk of bias evaluation was carried out independently by two investigators and disagreements were solved by consensus. The quality of the studies was assessed using the "Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [14]. The risk of bias was assessed using the Cochrane Collaboration tool, which considers six dimensions: random sequence generation, allocation concealment, blinding of participants and professionals, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting [15].

2.6 Statistical analysis

A random effects model was used for the Bayesian network meta-analysis (bNMA) [16]. Means and standard deviations were used to represent variables within the RCTs. All outcomes were expressed as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The analysis was performed using the Markov chain Monte Carlo methods. Three chains were suitable, yielding 5,000 iterations (20,000 per chain) and giving rise to the subsequent distributions of the model parameters. The Brooks-Gelman-Rubin method [17] was used for the convergence diagnostics. The model goodness of fit was assessed through the residual deviance. The I^2 statistic was used to investigate the statistical heterogeneity and a comparison-adjusted funnel plot

was used to identify any publication bias [18]. The 'node splitting' approach was adopted to measure the existing degree of inconsistency [18].

Aiming to explore the log HR association to achieve an ACR70 response, a meta-regression analysis was performed, wherein the ABA treatment effects depended on the study follow-up, on the presence of anti-TNF therapies in the control arm, and on the mean baseline HAQ score [16]. Sensitivity analysis was performed by excluding the trials with the longest exposure duration (in patient-years) by drug class. Statistical analyses were performed using the R Studio software, version 1.1.4 (R programming language, version 4.0.1 – R Foundation for Statistical Computing, Auckland, NZ).

3. RESULTS

Using the aforementioned search terms and platforms, we identified 600 citations: 320 in Medline (PubMed), 133 in Cochrane Library, 36 in Embase, 32 in Web of Science, 61 in Scopus, and 18 in LILACS. After excluding duplicates, 495 articles remained. We also excluded 391 articles based on their abstract and 81 articles based on the full text evaluation – mainly for not including TCZ, ABA, or RTX therapies and for being observational studies. We finished this extraction with 19 trials to be included for qualitative synthesis and meta-analysis. The PRISMA flowchart used for selecting studies can be found in **Supplementary Figure A.**

For our primary outcome meta-analysis, we included 19 RCTs with 7,835 patients (9,402 patient-years) randomized to the intervention arm (ABA with or without MTX [n = 1,742], RTX with or without MTX [n = 1,486], or TCZ with or without MTX [n = 1,583]) or to the control arm (placebo + MTX [n = 1,859] or anti-TNF with or without MTX [n = 1,165]).

The drugs RTX, TCZ, and ABA were compared with placebo in 13 clinical trials, being compared as adjuvant treatment with an active comparator (anti-TNF agent) in six other clinical trials. The mean age of patients included in the present study was 52.3 years; 77.2% of these patients were women; the mean disease duration was 8.7 years; and the mean follow-up was 1.2 years. Details of the basic trial characteristics are presented in **Supplementary Table B.**

Among the 19 selected trials, 31.5% (six) included TCZ as intervention arm, 31.5% (six) included RTX as active arm, and 31.5% (six) included ABA as intervention arm. Only one study compared ABA with RTX. **Supplementary Figure B** shows the network of direct comparisons among the treatment arms of included studies.

All studies had a low risk of bias according to the Cochrane Collaboration tool **(Supplementary Table C)** and were of high quality according to the GRADE system **(Supplementary Table D)**. As shown in **Supplementary Figure C.1-C.3,** there was no significant publication bias in funnel charts and no significant small-study bias according to the Egger tests.

3.1 ACR70

In the meta-analysis of random effects for the chance of achieving an ACR70 response at six months, six studies [19-24] with ABA therapy were selected. In these studies, 437 (25.6%) patients in the intervention arm and 250 (19.8%) patients in the control arm achieved an ACR70 response at six months and the observed HR was 1.35 (95% CI 1.17–1.55). For RTX, seven studies were selected [25-30], where 350 (23.5%) patients in the intervention arm and 107 (12%) patients in the control arm achieved an ACR70 response at six months, indicating a HR of 2.43 (95% CI 1.99–2.96). For TCZ, six studies were selected [31-36], with 294 (18.5%) patients in the

intervention arm and 97 (11%) patients in the control arm achieving an ACR70 response at six months, with a HR of 1.53 (95% CI 1.24–1.89) **(Supplementary Figure D.1).**

As shown in Table 1 and in Figure 1, direct and indirect comparisons suggest a superiority of ABA, TCZ, or RTX vs. placebo, with TCZ showing a slightly lower magnitude of effect (HR = 2.765, 95% CI 1.240–6.692) compared to ABA (HR = 3.423, 95% CI 1.422– 8.709) and to RTX (HR = 3.494, 95% CI 1.530–8.658). There was no statistical difference between these drugs and the anti-TNF therapy. For all analyses, there was a slight inconsistency between direct and indirect measures (Table 1, Indirect comparisons among bDMARDs), but they showed a substantial heterogeneity among RCTs (> 40%) **(Supplementary Figure D.1).**

3.2 ACR50

For the chances of achieving an ACR50 response, we selected the same studies as selected for the ACR70 response. For ABA, 730 (43%) patients in the intervention arm and 439 (34.7%) patients in the placebo arm were involved, with a HR of 1.28 (95% CI 1.17–1.41, $p < 0.001$, $I^2 = 54\%$, p for heterogeneity = 0.005). For RTX, 586 (39.4%) patients in the intervention arm and 201 (22.6%) patients in the control arm were involved, with a HR of 1.94 (95% CI 1.70–2.20, $p < 0.001$, $I^2 = 67\%$, p for heterogeneity = < 0.001). For TCZ, 537 (34%) patients in the intervention arm and 178 (20.3%) patients in the control arm were involved, with a HR of 1.75 (95% CI 1.52–2.02, $p < 0.001$, $I^2 = 79\%$, p for heterogeneity = < 0.001) **(Supplementary Figure D.2).**

Indirect comparisons among the intervention arms showed that ABA vs. RTX present a HR = 1.052 (95% CI 0.514–2.131), TCZ vs. RTX present a HR = 0.833 (95%

CI 0.378–1.835), and TCZ vs. ABA present a HR = 0.879 (95% CI 0.393–1.961) (Table 1).

3.3 ACR20

Finally, for the chances of achieving an ACR20 response, 1,108 (65%) patients in the intervention arm and 644 (51%) patients in the placebo arm were included for ABA, with a HR of 1.63 (95% CI 1.53–1.75, $p < 0.001$, $I^2 = 84\%$, p for heterogeneity < 0.001). For RTX, 880 (59.2%) patients in the intervention arm and 343 (38.5%) patients in the control arm were involved, with a HR of 1.75 (95% CI 1.61–1.91, $p < 0.001$, $I^2 = 71\%$, p for heterogeneity = < 0.001). For TCZ, 843 (53.2%) patients in the intervention arm and 292 (33.4%) patients in the control arm were involved, with a HR of 1.90 (95% CI 1.73–2.10, $p < 0.001$, $I^2 = 85\%$, p for heterogeneity = < 0.001) **(Supplementary Figure D.3).**

When indirectly compared to each other, ABA vs. RTX show a HR of 1.013 (95% CI 0.669–1.535) and TCZ vs. ABA show a HR of 1.014 (95% CI 0.626–1.618) (Table 1).

3.4 Explaining the heterogeneity among RCTs

The spider chart shown in Figure 2 presents an important imbalance among studies in the frequency of anti-TNF treatment in the control arm. RCTs with TCZ less often included anti-TNF agents in the intervention arm: ABA, 50%; RTX, 43%; and TCZ, 17% (p = 0.048). Besides, the baseline HAQ score was significantly lower (ABA 1.68 ± 0.15, RTX 1.68 ± 0.23, and TCZ 1.50 ± 0.17; p = 0.049). The mean follow-up time (total study duration) among RCTs was significantly longer in trials with ABA (25 ± 18.75 months) compared to those with RTX (9.43 ± 3.21) and TCZ (6.00 ± 0) (p =

0.015). Baseline 28-joint Disease Activity Score (DAS28) also showed an imbalance among trials, but this variable was excluded from the meta-regressions for presenting a high collinearity with the baseline HAQ score **(Supplementary Figure E.1)**.

3.5 Meta-regressions

Meta-regressions were conducted to assess the impact of treatments on the ACR70 response in a manner adjusted to the baseline HAQ score, study follow-up time (total study duration), and frequency of anti-TNF treatment in the control arm **(Supplementary Figure E.2)**.

These explanatory variables were chosen due to their association with the ACR70 response in univariate regressions and due to the existing imbalance among treatment arms in relation to these characteristics. As shown in Table 2, each 0.1 point over the mean baseline HAQ in each study was associated with a RR of 2.043 (95% CI 1.032–14.44, p for difference = 0.028, R^2 = 13%, I^2 = 89%, p for heterogeneity = < 0.001) for achieving an ACR70 response **(Supplementary Figure D.2)**. Additionally, the presence of an anti-TNF therapy in the control arm of any RCT was associated with a RR of 0.316 (95% CI 0.134–0.746, p for difference = 0.009, R^2 = 27%, I^2 = 85%, p for heterogeneity = < 0.001) **(Supplementary Figure D.1)** and each additional month of follow-up was associated with a RR of 0.980 (95% CI 0.961–0.996, p for difference = 0.048, R^2 = 9%, I^2 = 71%, p for heterogeneity = < 0.001) for achieving an ACR70 response.

In a multivariate model with the ACR70 response as an outcome and the covariates treatments in the intervention arm (RTX vs. ABA and TCZ vs. ABA), baseline HAQ score, follow-up time, and frequency of anti-TNF treatment in the control arm (Table 2), the heterogeneity was reduced (I^2 = 24%, p for heterogeneity = 0.27)

and the explanatory power of the model increased (R^2 = 85%). In this model, ABA did not modify the chance of achieving an ACR70 response when compared to RTX (1.773, 95% CI 0.113–10.21, p = 0.765). In contrast, ABA was associated with a RR of 2.217 (95% CI 1.554–3.161, p for difference = < 0.001) when compared to TCZ for achieving an ACR70 response. It means that, if the conditions of the RCTs were similar, ABA could increase the chance of achieving an ACR70 response by 2.22-fold when compared to TCZ.

3.6 Sensitivity analyses

Sensitivity analyses were performed considering the exclusion of the RCTs with the longest exposure durations (highest number of patient-years), one study being excluded for each class of non-anti-TNF biological drug. As shown in Table 1, the exclusion of such studies did not modify the results.

4. DISCUSSION

The present study showed no significant difference between tocilizumab, abatacept and rituximab to achieve ACR70 response in RCT and we also observed an abysmal imbalance in characteristics that increase or reduce the likelihood of achieving clinical response. The Bayesian network meta-analysis suggests an equivalence among treatments, as it compensates for the imbalances related to the treatment arms. However, it does not address the imbalances related to the duration of RCTs and to the baseline quality of life.

In meta-regressions, each increment of 0.1 point in the baseline HAQ score was associated with a 2-fold greater chance of achieving an ACR70 response, while such chance was reduced by 68% with the use of an anti-TNF therapy in the control arm

and by 2% with each additional follow-up month. As shown in the spider chart, ABA trials had a significantly longer duration compared to RTX and TCZ trials, while RCTs with ABA and RTX included anti-TNF agents in the control arm more frequently than the TCZ ones. Both these characteristics reduce the propensity of trials with ABA to drive an ACR70 response. Thus, in multivariate meta-regressions compensating for the effect of unbalanced characteristics, it is suggested that the use of ABA increases the chance of achieving an ACR70 response compared to the use of TCZ. However, it is important to understand that these are hypothesis-generating findings that need to be confirmed in a specific RCT.

The findings of our network meta-analysis comply with that of three previous meta-analyses [7-9]. Largely, comparisons among treatments were focused on the effectiveness of anti-TNF vs. non-anti-TNF agents. On the one hand, two of these studies showed a statistical power (1 – beta) > 80% for comparisons between anti-TNF and non-anti-TNF agents. On the other hand, comparisons among the three non-anti-TNF agents showed a statistical power < 65% (false negative probability higher than 35%). The present study reached a post-hoc statistical power for non-inferiority of 86.3% for the RTX vs. ABA comparison and of 99.2% for the TCZ vs. ABA comparison on the ACR70 response.

However, the presented result conflicts with that of observational studies, such as the study by Gottenberg et al. [37], where authors compared the effectiveness and safety of RTX, ABA, and TCZ in a population of patients with RA refractory to treatment with anti-TNF agents. The primary outcome of such study consisted of drug retention without the occurrence of death from any cause, discontinuation of the drug studied, initiation of a new biologic or a combination of conventional disease-modifying antirheumatic drugs or increase in the dose of oral corticosteroids at more than 10 mg

a day at two consecutive visits [37]. Among the main findings, RTX and TCZ had similar results, both being more effective in controlling the disease than ABA. Despite the evident reduction in the primary outcome and the better European League Against Rheumatism (EULAR) response with RTX and TCZ compared to ABA, there was no difference in terms of major outcomes, such as deaths, serious infections, cardiovascular events, and cancer.

The study by Gottenberg et al. [37] implemented techniques such as propensity score matching and inverse probability weighting, which made it possible to estimate the average treatment effects on each arm and to control the study arms for 28 confounding variables. However, an important concern related to the use of multiple imputation for missing data should be addressed. Although the technique is frequently used among data scientists and economists, the use of multiple imputations for large amounts of data is considered an important limitation in biomedical studies, since the data are simulated and do not accurately reflect what would be observed [38]. In the abovementioned paper [37], the missing data percentage reaches 30-50% of patients in one third of the adjustment variables, while the EULAR response was treated as missing data in 32-61% of patients. Besides, despite being a real-world study with data from 2005-2015, the outcomes were established over a 24-month horizon. Though it is longer than the duration of clinical trials (6-12 months), this is still insufficient to represent the average life expectancy of patients with RA. Thus, the findings of this observational study have important limitations.

The comparison among non-anti-TNF agents is essential for choosing the ideal anti-inflammatory strategy. Additionally, it contributes to cost-effectiveness analyses establishing which drug could bring the best balance between gains in quality of life and morbidity reduction in relation to the costs of therapies [39]. However, when

therapies have a similar efficacy, it is worth minimizing the risk of false negative results [40]. Through the present study, it is possible to conclude that ABA, TCZ, and RTX have a similar efficacy when accounting solely the effects of co-treatments, but when accounting the full spectrum of unbalanced factors across RCT arms, our findings suggest that ABA increases the chance of achieving an ACR70 response in comparison to TCZ.

This study further exemplifies why it is essential to comprehensively understand the heterogeneity among studies. Though meta-regression results should be understood as a hypothesis-generating evidence, they enable testing a scenario where components of heterogeneity among RCTs become more balanced.

4.1 Limitations

Some important limitations must be emphasized. During the extraction of information from the studies, some data were not available for all trials, and the analysis of only English published trials can generate a systematic data collection bias. In general, unpublished studies and observational studies could have a different impact on the results; however, there is great heterogeneity in terms of selection and statistical treatment in observational studies, which could hinder the data analysis.

In contrast, there are two important issues to be considered as limitations to the interpretation of these results. Firstly, there is a high degree of heterogeneity among studies for all drugs. The high variability in the relative treatment effects threatens the external validity of the study evidence and limits its generalization [41]. Secondly, the network meta-analysis does not compensate for other factors unrelated to the drugs that make up the treatment arms [42]. When adjusted to the baseline quality of life, follow-up time, and presence of anti-TNF therapies in the control arm, meta-

regressions showed that the use of ABA increased the chance of achieving an ACR70 response by 2.2-fold compared to the use of TCZ, with a low heterogeneity and a high explanatory power (R^2 > 80%).

Another limitation of our study was our inability to ascertain the reasons for anti-TNF agent or MTX failure and the number of prior anti-TNF therapy failures. Patients may have been treated with different doses or for different anti-TNF treatment durations before considering an IR. Another potential limitation is the number of comparisons made for this analysis, which may favor spurious associations. However, the statistical power achieved in this study suggests that chances of false negative results are extremely low.

Additionally, we did not evaluate the impact of different dosing or posology used across RCTs to improve the clustering. Yet, considering the broad inclusion criteria, which resulted in a study population that best resembles real patients, and the choice of viable interventions, in the case of clinical trials, the results of this study have external validity with applicability in daily practice.

5. CONCLUSION

In this study, a systematic review was carried out using a network meta-analysis to compare the efficacy of RTX, TCZ, and ABA in individuals with RA refractory to treatment with anti-TNF agents or MTX. The network meta-analysis showed no significant difference among the studied drugs in achieving an ACR70 response, therefore, they have a similar effectiveness, with low inconsistency, but high heterogeneity among studies. Based on the result of multivariate meta-regressions, by mathematically equalizing the conditions of the RCTs, we estimate that ABA could increase the chance of reaching an ACR70 response by 2.2-fold compared to TCZ.

DECLARATION OF COMPETING INTEREST

The authors disclose no conflicts of interest.

FUNDING

This work was supported by grants 437413/2018-7 from the Brazilian National Research Council (CNPq) and 2019/09068-3 from São Paulo State Foundation for Research (FAPESP).

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FIGURE CAPTIONS

Figure 1. Hazard ratios for American College of Rheumatology 20%, 50% or 70% improvement (ACR20 [a], ACR50 [b] or ACR70 [c]) response rate at the end of follow-up. The estimates represent the pooled direct and indirect comparisons between non-anti-TNF biologics (abatacept, rituximab and tocilizumab), anti-TNF biologics and placebo.

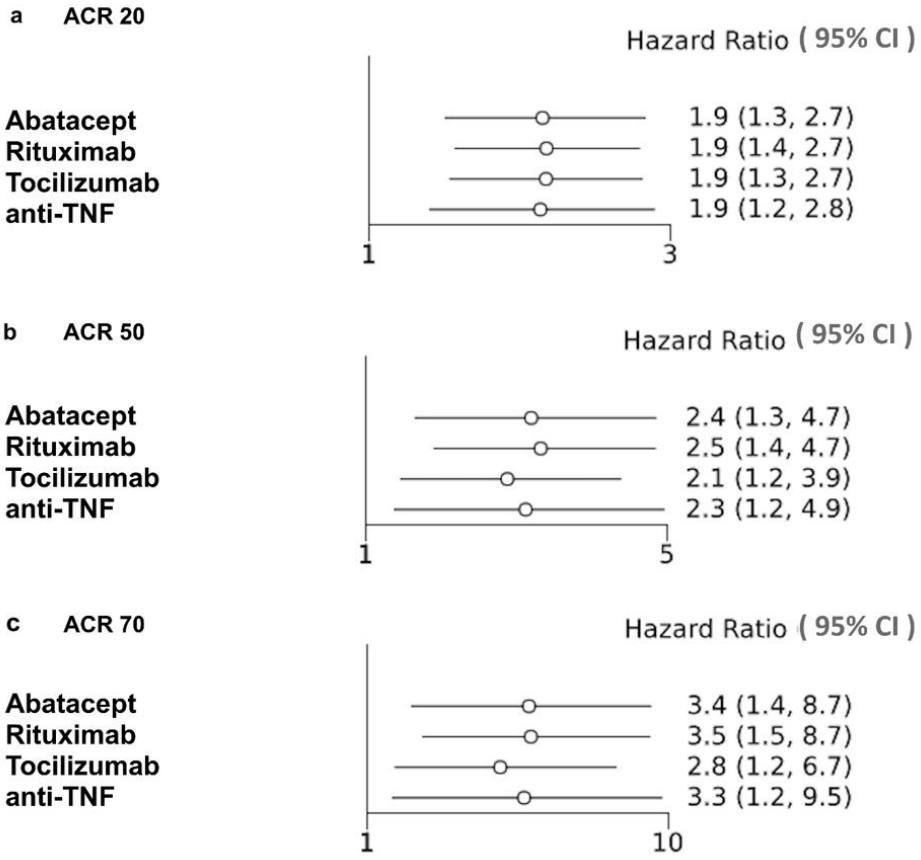

Figure 2. The Spider chart describes the imbalance among RCTs characteristics included in the meta-analysis according to the non-anti-TNF treatment used in active arm (ABA, RTX or TCZ). The suffix "_posit.vs.ACR70" represent the independent variables that show positive association with ACR70 response, and the suffix

"_neg.vs.ACR70" represent the independent variables that show negative association with ACR70 response.

Example: the higher the follow-up time (suffix "_neg.vs.ACR70"), the lower the chance of achieving ACR70 response.

Followup.t: follow-up time (total study duration); ACR70: 70% achieving ACR response; ACR50: 50% achieving ACR response; ACR20: 20% achieving ACR response.

Background anti-TNF: percentage of individuals on tumor necrosis factor (TNF) inhibitors; HAQ: Health Assessment Questionnaire score; ABA: abatacept; RTX: rituximab; TCZ: tocilizumab; ACR: American College of Rheumatologists.

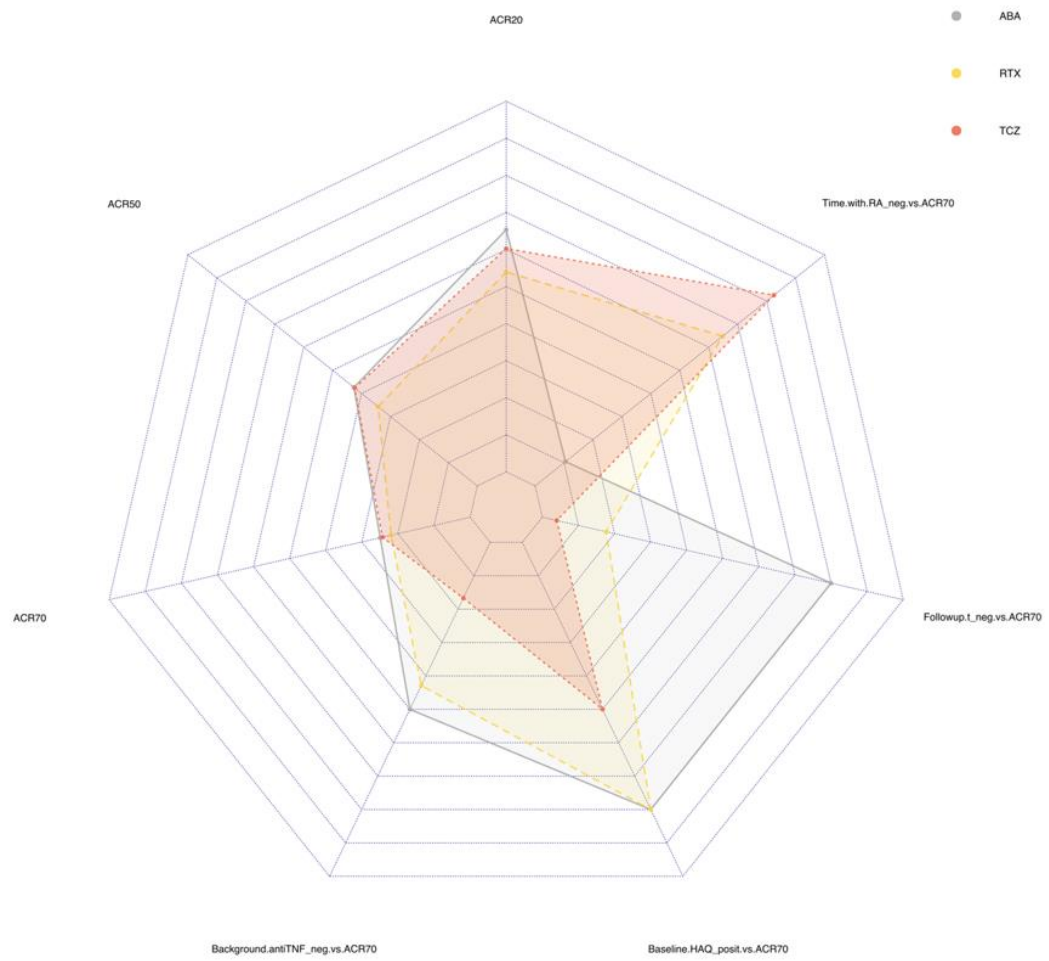

Table 1. Indirect comparisons among bDMARDs in active rheumatoid arthritis expressed in hazard ratios for achieving 70% of American College of Rheumatology response at six months with sensitive analyses

	ACR70 response rate, HR (95% CI), p value	
	All trials	**Excluding one trial from each class***
Abatacept vs Rituximab	1.017 (0.373, 2.845), p=0.84	1.029 (0.324, 2.959), p=0.88
Tocilizumab vs Rituximab	0.791 (0.254, 2.461), p=0.32	0.811 (0.224, 2.618), p=0.40
Tocilizumab vs Abatacept	0.806 (0.263, 2.505), p=0.37	0.814 (0.237, 2.614), p=0.43
Abatacept vs anti-TNF	1.043 (0.422, 2.242), p=0.59	1.063 (0.402, 2.492), p=0.56
Tocilizumab vs anti-TNF	0.839 (0.373, 3.804), p=0.45	0.814 (0.331, 4.007), p=0.41
Rituximab vs anti-TNF	1.059 (0.339, 2.581), p=0.51	1.042 (0.305, 2.886), p=0.67
Abatacept vs placebo	3.423 (1.422, 8.709), p<0.001	3.438 (1.413, 8.762), p<0.001
Tocilizumab vs placebo	2.765 (1.240, 6.692), p=0.009	2.525 (1.096, 6.921), p=0.015
Rituximab vs placebo	3.494 (1.530, 8.658), p<0.001	3.509 (1.522, 8.676), p<0.001

* Sensitivity analysis: excluding trials with largest exposure (in patient-years) from each class

Random effects standard deviation for all trials 0.854 (0.537, 1.408), Inconsistency factor (distance between direct and indirect effects) are 0.021 (-2.661, 2.607, p=0.988), 0.032 (-2.592, 2.557, p=0.934), 0.038 (-2.711, 2.557, p=0.984), -1.247 (-3.628, 1.148 p=0.271), -1.028 (-3.924, 1.018 p=0.176), 0.150 (-1.764, 2.109, p=0.879), 0.714 (-1.353, 2.751, p=0.468), -1.278 (-3.576, 1.094, p=0.248), 0.666 (-1.304, 2.635, p=0.476), respectively for the node-split comparisons Abatacept vs Rituximab, Tocilizumab vs Rituximab, Tocilizumab vs Abatacept, Abatacept vs anti-TNF, Tocilizumab vs anti-TNF, Rituximab vs anti-TNF, Abatacept vs placebo, Tocilizumab vs placebo, Rituximab vs placebo. For ACR70 network meta-analysis model fit statistics posterior mean of the residual deviance (D_{res}=40.1), and deviance information criterion (DIC) = 77.1.

TNF:tumor necrosis factor; HR: hazard ratio; ACR70: 70% of American College of Rheumatology.

Table 2. Meta-regression models for achieving 70% of American College of Rheumatology response at total of study duration (mean = 14 months) as dependent variable

	RR	95% CI		p
		Lower bound	Upper bound	
Model 1				
Mean baseline HAQ (each additional 0.1 point)	2.0433	1.0328	14.4460	0.028
Model 2				
Background anti-TNF in control arm (yes vs no)	0.3166	0.1345	07460	0.009
Model 3				
Follow-up time (each additional 1 month)	0.9714	0.9522	0.9920	0.007
Model 4				
Mean baseline HAQ (each additional 0.1 point)	2.0332	1.0141	14.6164	0.045
Background anti-TNF in control arm (yes vs no)	0.2187	0.1341	0.3567	<0.001
Follow-up time (each additional 1 month)	0.9763	0.9504	0.9899	0.016
ABA vs RTX	1.7736	0.1134	10.2165	0.625
ABA vs TCZ	2.2171	1.5541	3.1614	<0.001

RR: relative risk; HAQ: Health Assessment Questionnaire score; TNF, tumor necrosis factor; ABA: abatacept; RTX: rituximab; TCZ: tocilizumab; ACR70: 70% of American College of Rheumatology

APÊNDICE A

Citation

Amanda Borges Oliveira, Luiz Sergio F de Carvalho F de Carvalho. The Impact on Cost, effectiveness and safety of Rituximab, Abatacept, Tocilizumab in Patients With Rheumatoid Arthritis Refractory to Treatment with ANTI-TNF Agents: a systematic review and meta-analyzis. PROSPERO 2020 CRD42020167953 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020167953

Review question

In patients with rheumatoid arthritis refractory to treatment with anti-TNF agents, what is the cost, effectiveness and safety of the use of Rituximab, Abatacept and Tocilizumab?

Searches

1. PubMed

2. Cochrane

3. LILACS

4. Web of Science

5. Scopus

6. EMBASE

Date: 18/01/2020

Types of study to be included

Randomized Controlled Trial.

Condition or domain being studied

Rheumatoid arthritis (RA) is a systemic, chronic and progressive inflammatory disease that primarily affects the synovial membrane of the joints and can lead to bone and cartilaginous destruction (1). It is considered one of the most common autoimmune diseases worldwide (2). In Brazil, the prevalence is 0.2 to 1.0%, totaling 400 thousand to 2 million people affected by RA (3). The impact of the disease is due to increased disability and reduced quality of life (4), which reflects a disease with considerable cost in terms of medical care and social aspects (5).

The diagnosis of RA is established considering clinical findings and complementary exams. No single test, whether laboratory, imaging or histopathological, can confirm the diagnosis (6).

Considering that it is an autoimmune disease, rheumatoid arthritis has no cure. Thus, the goal of treatment is to control inflammation, reduce pain, prevent disease progression and structural damage, preserve functional capacity and improve the quality of life of individuals.

Participants/population

Patients with rheumatoid arthritis refractory to treatment with anti-TNF agents.

Intervention(s), exposure(s)

Rituximab, Abatacept and Tocilizumab

Comparator(s)/control

Rituximab, Abatacept, Tocilizumab and placebo.

Context

1. literature review;

2. Editorials?Letters;

3. Conferences, Summaries and Annals;

4. In vitro studies;

5. Studies of animal models;

6. Qualitative studies;

7. Cross-sectional studies;

8. Case-control studies;

9. Systematic reviews, overview and scoop reviews;

10. Alternative Treatments: antibiotics;

11. Studies not including Rituximab or Abatacept or Tocilizumab;

12. Studies with exposure time less than 12 months or 48 weeks;

13. Patients with other types auto-immune diseases;

14. Studies evaluating the use of tocilizumab, rituxumab or abatacept for other diseases;

15. Co-morbidities: pregnant, nursing, histoplasmosis, coccidiomycosis, HIV, Tuberculosis etc;

16. Patients with hypersensitivity to Rituximab or Abatacept or Tocilizumab;

Main outcome(s)

Data collected will include study design (rescue, primary and secondary endpoints, intention to treat (ITT) analysis, follow-up, number of completers), baseline characteristics (gender, age, disease duration, proportion of rheumatoid factor, previous DMARDs), study intervention and concomitant treatments. As primary outcome, we chose the ACR50 response rate (at least 50% improvement according to the American College of Rheumatology criteria in the number of swollen and tender joints, and in three of the following five parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C reactive protein or erythrocyte sedimentation rate and the Health Assessment Questionnaire (HAQ score) at 24–30 weeks).

Measures of effect

Data collected will include study design (rescue, primary and secondary endpoints, intention to treat (ITT) analysis, follow-up, number of completers), baseline characteristics (gender, age, disease duration, proportion of rheumatoid factor, previous DMARDs), study intervention and concomitant treatments. As primary outcome, we chose the ACR50 response rate (at least 50% improvement according to the American College of Rheumatology criteria in the number of swollen and tender joints, and in three of the following five parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C reactive protein or erythrocyte sedimentation rate and the Health Assessment Questionnaire (HAQ score) at 24–30 weeks).

Additional outcome(s)

'Not applicable'

Measures of effect

'Not applicable'

Data extraction (selection and coding)

Studies will be selected according to the defined search strategy. The search terms will be inserted in the following websites: Cochrane, Web of Science, LILACS, PubMed, Embase and Scopus. From this survey, the studies will be classified with Article Manager, applying the exclusion criteria. Subsequently, from studies with people with rheumatoid arthritis, data such as age, sex, color, pathologies, time of medication use will be extracted in an Excel spreadsheet, and after data will be transferred to Stata for statistical analyses.

Data collected will include study design (rescue, primary and secondary endpoints, intention to treat (ITT) analysis, follow-up, number of completers), baseline characteristics (gender, age, disease duration, proportion of rheumatoid factor, previous DMARDs), study intervention and concomitant treatments. As primary outcome, we chose the ACR50 response rate (at least 50% improvement according to the American College of Rheumatology criteria in the number of swollen and tender joints, and in three of the following five parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C reactive protein or erythrocyte sedimentation rate and the Health Assessment Questionnaire (HAQ score) at 24–30 weeks).

Risk of bias (quality) assessment

We will assess the risk of bias by using standard methods such as funnel plot and Egger tests for each of the selected variables in the study.

Strategy for data synthesis

After including & excluding studies according to the quality appraisal, the analysis of data & results will initially begin with a descriptive evaluation of each study, which will be presented in a table. If the study results are very heterogeneous, we will summarize the data narratively. Using Cochrane's Q, we will test for heterogeneity between studies (significant if $p<0.10$) and quantified the extent of variability between studies due to heterogeneity instead of chance with I^2 (ranging from 0% to 100%). If study results are not heterogeneous ($I^2 < 50\%$), we will proceed with the statistical analyses (meta-analysis). The analyses will include numerical and graphical presentations of the data (summary tables and forrest plots). As primary outcome, we chose the ACR50 response rate. We will evaluate the strength and consistency of the evidence by using both random and fixed effects as well as Funnel plots and Egger bias tests. If we find inconsistencies we will investigate the reasons for that. Metaregressions will be performed in order to evaluate the impact of age, disease duration, proportion of rheumatoid factor, previous DMARDs on ACR50 response rate.

Analysis of subgroups or subsets

We will perform three separate analyses: one only with RCTs, one only with observational studies, and one including both RCTs and observational studies.

Contact details for further information

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Organisational affiliation of the review

FEPECS

Review team members and their organisational affiliations

Ms Amanda Borges Oliveira. FEPECS
Mr Luiz Sergio F de Carvalho F de Carvalho. FEPECS

Type and method of review

Cost effectiveness, Meta-analysis, Systematic review

Anticipated or actual start date

26 September 2019

Anticipated completion date
31 August 2020

Funding sources/sponsors
None

Conflicts of interest

Language
English

Country
Brazil

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
28 April 2020

Date of first submission
04 February 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
28 April 2020

APÊNDICE B

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***3***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note*	***5***

		whether any have been clustered or merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl pg 28
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	7
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7,8

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***8***
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***Suppl pg 32***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***Suppl pg 29***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	***Suppl file 29***
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Suppl pg 30
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	Suppl pg 31
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***8, 9***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values	***11***

		from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	10
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***8, 9, 10, 11***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	13,14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***17***

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicate wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

ANEXOS

Supplementary file 1

Table A: Search strategy

PICOS		Key Words
Types of participants (P)	Patients with rheumatoid arthritis refractory to treatment with anti-TNF agents	(Men OR Man OR Boy OR Boys OR Girls OR Girl OR Woman OR Womans OR "Women's Groups" OR "Women Groups" OR Women OR Womens OR Human OR Humans) AND (Arthritis OR "Rheumatoid Arthritis" OR "Arthritis, Rheumatoid" OR "Rheumatoid Arthritis Refractory") AND ("Receptors, Tumor Necrosis Factor" OR "Receptors, Cachectin" OR "Tumor Necrosis Factor Receptors" OR "TNF Receptor" OR "Receptor, TNF" OR "TNF Receptors" OR "Tumor Necrosis Factor Receptor" OR "Cachectin Receptors" OR "Receptors, TNF" OR Adalimumab OR Humira OR "Adalimumab-adbm" OR Amjevita OR "Adalimumab-atto" OR Cyltezo OR "D2E7 Antibody" OR "Antibody, D2E7" OR Infliximab OR "Monoclonal Antibody Ca2" OR "CA2, Monoclonal Antibody" OR "MAb cA2" OR "Infliximab-abda" OR Renflexis OR "Infliximab-dyyb" OR Inflectra OR Remicade OR "Anti–Tumor Necrosis Factor Therapy" OR "Tumour necrosis factor α ")
Types of interventions (I)	Rituximab, Abatacept and Tocilizumab	(Rituximab OR "CD20 Antibody, Rituximab" OR "Rituximab CD20 Antibody" OR Mabthera OR "IDEC-C2B8 Antibody" OR "IDEC C2B8 Antibody" OR "IDEC-C2B8" OR "IDEC C2B8" OR "GP2013" OR Rituxan OR "B-Cell–Targeted Therapy") OR (Abatacept OR Belatacept OR Orencia OR Nulojix OR "CTLA-4-Ig" OR "Cytotoxic T Lymphocyte-Associated Antigen 4-Immunoglobulin" OR "Cytotoxic T Lymphocyte Associated Antigen 4 Immunoglobulin" OR "CTLA4-Ig" OR "CTLA4-Ig Immunoconjugate" OR "CTLA4 Ig Immunoconjugate" OR "Immunoconjugate, CTLA4-Ig" OR "CTLA4-Fc") OR (Tocilizumab OR atlizumab OR "monoclonal antibody, MRA" OR Actemra OR "Organotechnetium Compounds" OR "Antibodies, Monoclonal, Humanized")
Comparison (C)		
Types of outcome measures (O)	Cost, effectiveness and safety	("Costs, Cost Analysis" OR "Cost, Cost Analysis" OR "Costs and Cost Analyses" OR "Cost Analysis" OR "Analysis, Cost" OR "Analyses, Cost" OR "Cost Analyses" OR "Cost Comparison" OR "Comparison, Cost" OR "Comparisons, Cost" OR "Cost Comparisons" OR Affordability OR Affordabilities OR "Cost-Minimization Analysis" OR "Analyses, Cost-Minimization" OR "Analysis, Cost-Minimization" OR "Cost Minimization Analysis" OR "Cost-Minimization Analyses" OR Pricing OR Cost OR Costs OR "Cost Measures" OR "Cost Measure" OR "Measure, Cost" OR "Measures, Cost" OR "Cost, Drug" OR "Costs, Drug" OR "Drug Cost") OR (Efficiency OR Productivity) OR (Safety OR Safeties OR Placebos OR "Effect, Placebo" OR "Effects, Placebo" OR "Placebo Effects" OR "Drug Withdrawal, Safety-Based" OR

		“Drug Withdrawals, Safety-Based” OR “Safety Based Drug Withdrawals” OR “Drug Withdrawals Due to Safety” OR “Safety-Based Drug Withdrawal” OR “Safety Based Drug Withdrawal” OR “Drug Withdrawal Due to Safety”)
Types of studies (S)	RCTs	"Randomized Controlled Trial" OR "Clinical Trials, Randomized" OR "Trials, Randomized Clinical" OR "Controlled Clinical Trials, Randomized" OR “Cohort Study” OR “Studies, Cohort” OR “Study, Cohort” OR “Concurrent Studies” OR “Studies, Concurrent” OR “Concurrent Study” OR “Study, Concurrent” OR “Closed Cohort Studies” OR “Cohort Studies, Closed” OR “Closed Cohort Study” OR “Cohort Study, Closed” OR “Study, Closed Cohort” OR “Studies, Closed Cohort” OR “Analysis, Cohort” OR “Cohort Analysis” OR “Analyses, Cohort” OR “Cohort Analyses” OR “Historical Cohort Studies” OR “Cohort Study, Historical” OR “Historical Cohort Study” OR “Study, Historical Cohort” OR “Cohort Studies, Historical” OR “Studies, Historical Cohort” OR “Incidence Studies” OR “Incidence Study” OR “Studies, Incidence” OR “Study, Incidence”

Supplementary file 2

Table B: Characteristics of baseline studies

First author	Publication (year)	Sample size (N)	Study duration (months)	% female	Age (years)	Time with RA (years)	Concomitant therapy	Active treatment	Control treatment	Other comparator	MTX dose/ week	Refractory to
1. SWITCH	2018	122	12	83.6	56.7	6.7	MTX	ABA	Anti-TNF	RTX	15mg	MTX
2. Bijlsma et al	2016	317	6	67	54	0	MTX	TCZ	Placebo	-	30mg	MTX
3. ORBIT	2016	295	12	72	57	7.2	-	RTX	Anti-TNF	-		MTX
4. Gaultney et al	2016	636	24	81.7	51.2	1.8	MTX	ABA	Anti-TNF	-	17mg	MTX
5. Lindegaard et al	2016	47	6	78.7	58.6	12.5	MTX	TCZ	Placebo	-	22mg	Anti TNF
6. Kivitz et al	2014	656	6	84.7	52	11.1	MTX	TCZ	Placebo	-		Anti TNF
7. AMPLE	2014	646	24	81.7	51.2	1.8	MTX	ABA	Anti-TNF	-	17.5mg	MTX
8. ADACTA	2013	325	6	80.6	53.8	6.8	MTX	TCZ	Anti-TNF	-		MTX

9. ATTAIN	2012	317	60	77.6	52.9	11.5	MTX	ABA	Placebo	-		Anti TNF
10. ATTEST	2011	321	24	82.5	49	7.6	MTX	ABA	Anti-TNF	-		MTX
11. Greenwald et al	2011	51	6	88.2	50.4	10.5	MTX	RTX	Placebo	-	25mg	----
12. SERENE	2010	509	12	82.1	52.3	7.1	MTX	RTX	Placebo	-	25mg	MTX
13. SUNRISE	2010	475	12	80.2	54	11.5	MTX	RTX	Placebo	-	25mg	MTX
14. RADIATE	2008	489	6	81	52.7	11.6	MTX	TCZ	Placebo	-	16.5mg	Anti TNF
15. REFLEX	2008	499	24	81	52.5	11.9	MTX	RTX	Placebo	-	25mg	Anti TNF
16. OPTION	2008	622	6	82	51	7.5	MTX	TCZ	Placebo	-	25mg	MTX
17. Emery et al	2006	465	6	80	51.2	10.4	MTX	RTX	Placebo	-	25mg	Anti TNF
18. Kremer et al	2006	652	12	78.8	50.9	8.7	MTX	ABA	Placebo	-	16.1mg	MTX
19. Genovese et al	2005	391	6	78	53.5	11.8	MTX	ABA	Placebo	-	15.2mg	Anti TNF

Supplementary file 3

Table C: Risk of bias of individual randomized controlled trials

	Risk of Bias						
First author	**Random sequence generation**	**Alocation Concealment**	**Blinding of patients, personnel**	**Blinding of outcome assessors**	**Incomplete outcome data**	**Selective outcome reporting**	**Others**
1. SWITCH	Low	Low	Low	Low	Low	Unclear	Low
2. Bijlsma et al	Low	Low	Low	Low	Unclear	Low	Low
3. ORBIT	Low	Unclear	Low	Low	Low	Low	Low
4. Gaultney et al	Low	Low	Low	Low	Unclear	Unclear	Low
5. Lindegaard et al	Low	Unclear	Low	Low	Low	Low	Low
6. Kivitz et al	Low	Low	Low	Low	Low	Low	Low
7. AMPLE	Low	Low	Low	Low	Low	Low	Low

8. ADACTA	Low	Unclear	Low	Low	Low	Low	Low
9. ATTAIN	Low	Low	Low	Low	Low	Low	Low
10. ATTEST	Low	Unclear	Low	Low	Low	Low	Low
11. Greenwald et al	Unclear	Low	Low	Low	Low	Low	Unclear
12. SERENE	Low	Low	Low	Low	Low	Low	Low
13. SUNRISE	Low	Low	Low	Low	Low	Low	Low
14. RADIATE	Low	Low	Low	Low	Low	Low	Low
15. REFLEX	Low	Low	Low	Low	Low	Low	Unclear
16. OPTION	Low	Low	Low	Low	Low	Low	Low
17. Emery et al	Low	Low	Low	Low	Low	Low	Unclear
18. kremer et al	Low	Low	Low	Low	Low	Low	Low
19. Genovese et al	Low	Unclear	Low	Low	Low	Low	Low

Supplementary file 4

Table D: GRADE: Efficacy among rituximab, tocilizumab and abatacept in individuals with rheumatoid arthitis refractory to treatment with anti-TNF agents of MTX

Number of studies	Study design	Certainty assessment				Other considerations	Number of patients		Effect		Certainty
		Risk of bias	Inconsistency	Indirect evidence	Imprecision		[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)	
American College of Rheumatology - ACR70 (follow-up: 25 months; evaluated using: ABATACEPT)											
6	randomized clinical trials	not serious	not serious	not serious	not serious	none	437/1701 (25.7%)	250/1262 (19.8%)	**HR 1.35** (1.17 to 1.55)	**60 plus to 1.000** (from 30 plus to 92 plus)	⊕⊕⊕⊕ HIGH
American College of Rheumatology - ACR70 (follow-up 9,43 months; evaluated using: RITUXIMAB)											

Number of studies	Study design	Certainty assessment				Other considerations	Number of patients		Effect		Certainty
		Risk of bias	Inconsistency	Indirect evidence	Imprecision		[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)	
7	randomized clinical trials	not serious	not serious	not serious	not serious	none	350/1486 (23.6%)	107/889 (12.0%)	**HR 2.43** (1.99 to 2.96)	**147 plus to 1.000** (from 105 plus to 196 plus)	⊕⊕⊕⊕ HIGH
American College of Rheumatology - ACR70 (follow-up: 6 months; evaluated using: TOCILIZUMAB)											
6	randomized clinical trials	not serious	not serious	not serious	not serious	none	294/1583 (18.6%)	97/873 (11.1%)	**HR 1.53** (1.24 to 1.89)	**54 plus to 1.000** (from 25 plus to 88 plus)	⊕⊕⊕⊕ HIGH
American College of Rheumatology - ACR50 (follow-up: 25 months; evaluated using: ABATACEPT)											
6	randomized clinical trials	not serious	not serious	not serious	not serious	none	730/1701 (42.9%)	439/1262 (34.8%)	**HR 1.28** (1.17 to 1.41)	**74 plus to 1.000** (from 46 plus to 105 plus)	⊕⊕⊕⊕ HIGH
American College of Rheumatology - ACR50 (follow-up: 9.43 months; evaluated using: RITUXIMAB)											

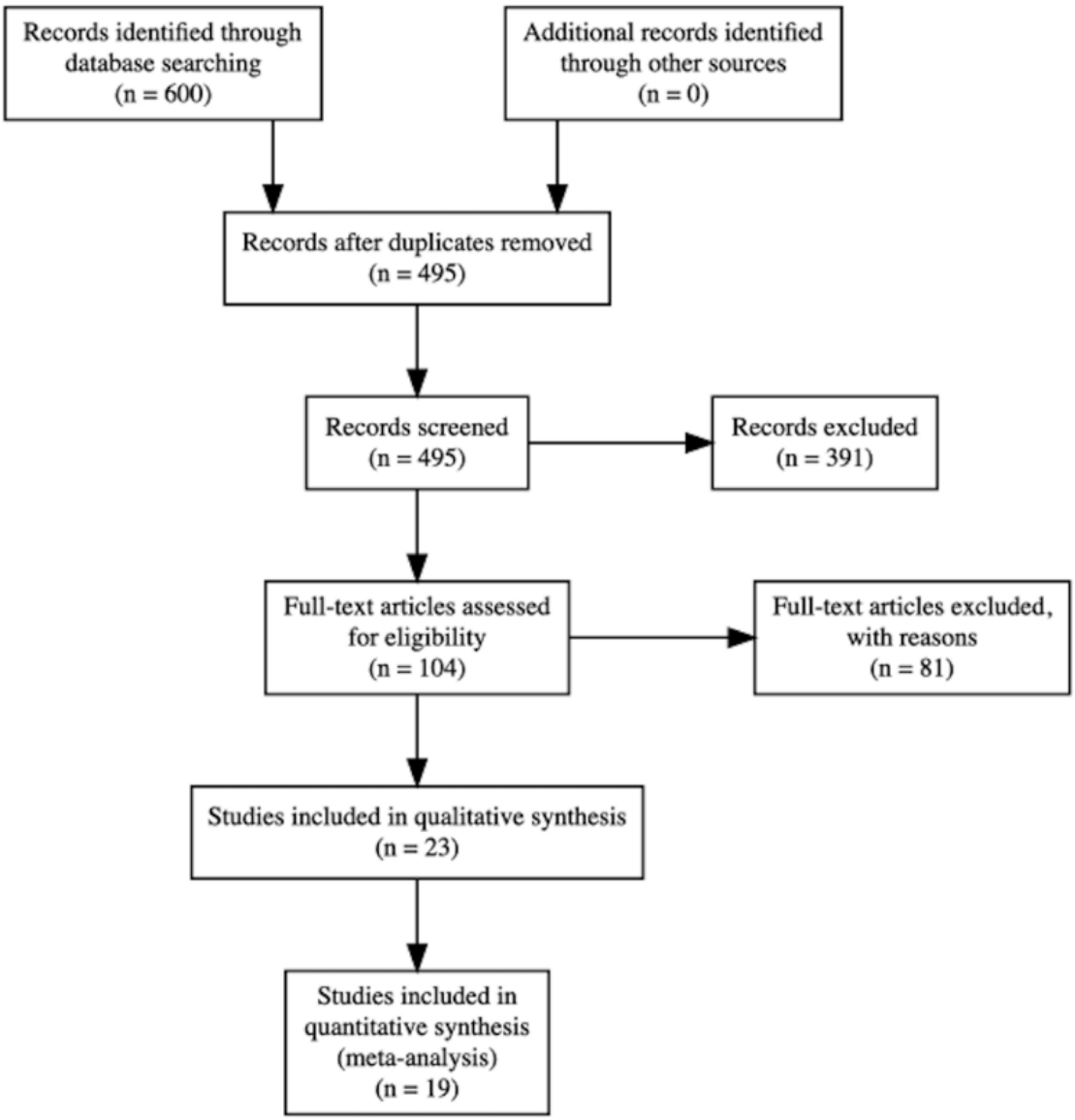
Number of studies	Study design	Certainty assessment				Other considerations	Number of patients		Effect		Certainty
		Risk of bias	Inconsistency	Indirect evidence	Imprecision		[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)	
7	randomized clinical trials	not serious	not serious	not serious	not serious	none	586/1486 (39.4%)	201/889 (22.6%)	**HR 1.94** (1.70 to 2.20)	**166 plus to 1.000** (from 127 plus to 205 plus)	⊕⊕⊕⊕ HIGH
American College of Rheumatology - ACR50 (follow-up: 6 months; evaluated using: TOCILIZUMAB)											
6	randomized clinical trials	not serious	not serious	not serious	not serious	none	537/1583 (33.9%)	178/873 (20.4%)	**HR 1.75** (1.52 to 2.02)	**125 plus to 1.000** (from 89 plus to 165 plus)	⊕⊕⊕⊕ HIGH
American College of Rheumatology - ACR20 (follow-up: 25 months; evaluated using: ABATACEPT)											
6	randomized clinical trials	not serious	not serious	not serious	not serious	none	1108/1701 (65.1%)	644/1262 (51.0%)	**HR 1.63** (1.53 to 1.75)	**177 plus to 1.000** (from 154 plus to 203 plus)	⊕⊕⊕⊕ HIGH

Number of studies	Study design	Certainty assessment				Other considerations	Number of patients		Effect		Certainty
		Risk of bias	Inconsistency	Indirect evidence	Imprecision		[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)	
American College of Rheumatology - ACR20 (follow-up: 9.43 months; evaluated using: RITUXIMAB)											
7	randomized clinical trials	not serious	not serious	not serious	not serious	none	880/1486 (59.2%)	343/889 (38.6%)	**HR 1.75** (1.61 to 1.91)	**188 plus to 1.000** (from 158 plus to 220 plus)	⊕⊕⊕⊕ HIGH
American College of Rheumatology - ACR20 (follow-up: 6 months; evaluated using: TOCILIZUMAB)											
6	randomized clinical trials	not serious	not serious	not serious	not serious	none	843/1583 (53.3%)	292/873 (33.4%)	**HR 1.90** (1.73 to 2.10)	**204 plus to 1.000** (from 171 plus to 240 plus)	⊕⊕⊕⊕ HIGH

CI: Confidence interval; **HR:** Hazard Ratio

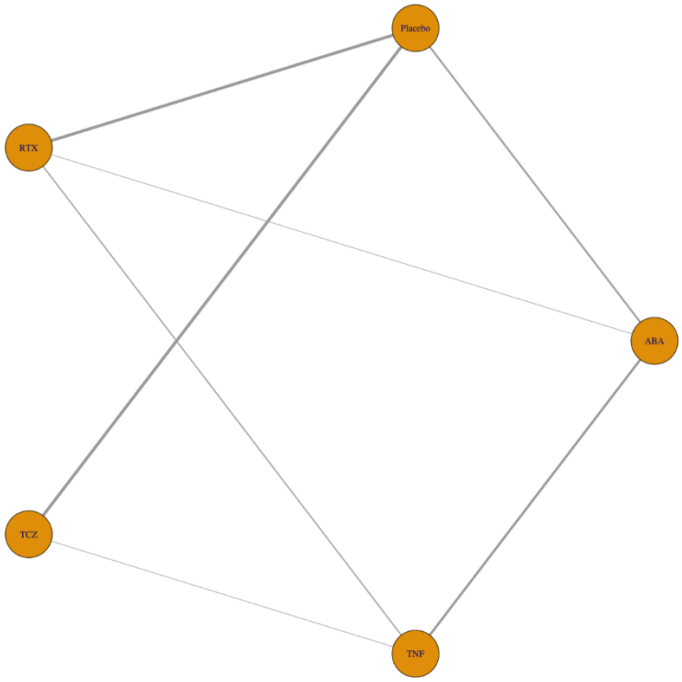
Supplementary file 5

Figure A: Direct combinations of studies included



Supplementary file 6

Figure B: Study network show dense connections between placebo and the bDMARDS abatacept (ABA), rituximab (RTX) and tocilizumab (TCZ). Anti-TNF therapies are also connected to abatacept, rituximab and tocilizumab. However, direct connection among non-anti-TNF bDMARDs is only present between RTX vs ABA and no connections between TCZ vs RXT or between TCZ vs ABA



Supplementary file 7

Figure C.1. Funnel plot for ACR 20 response

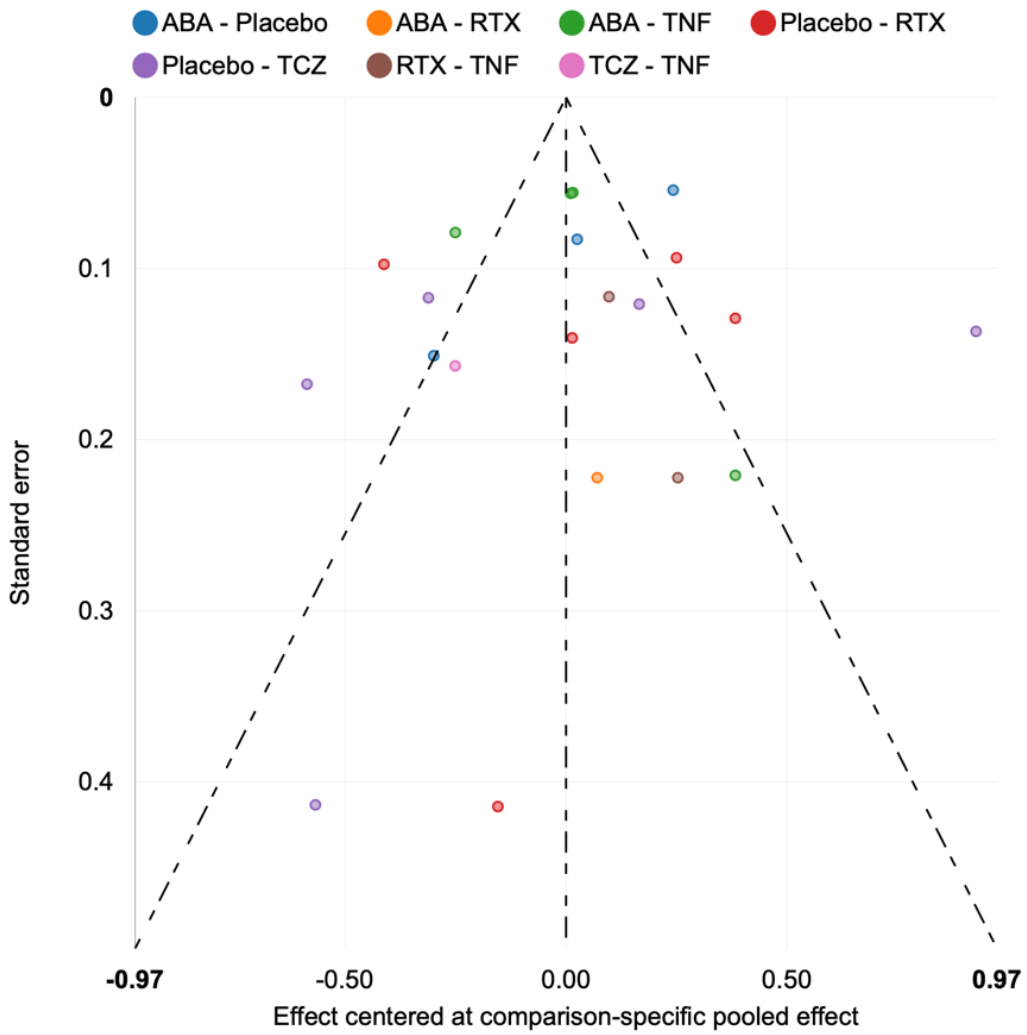


Figure C.2. Funnel plot for ACR 50 response

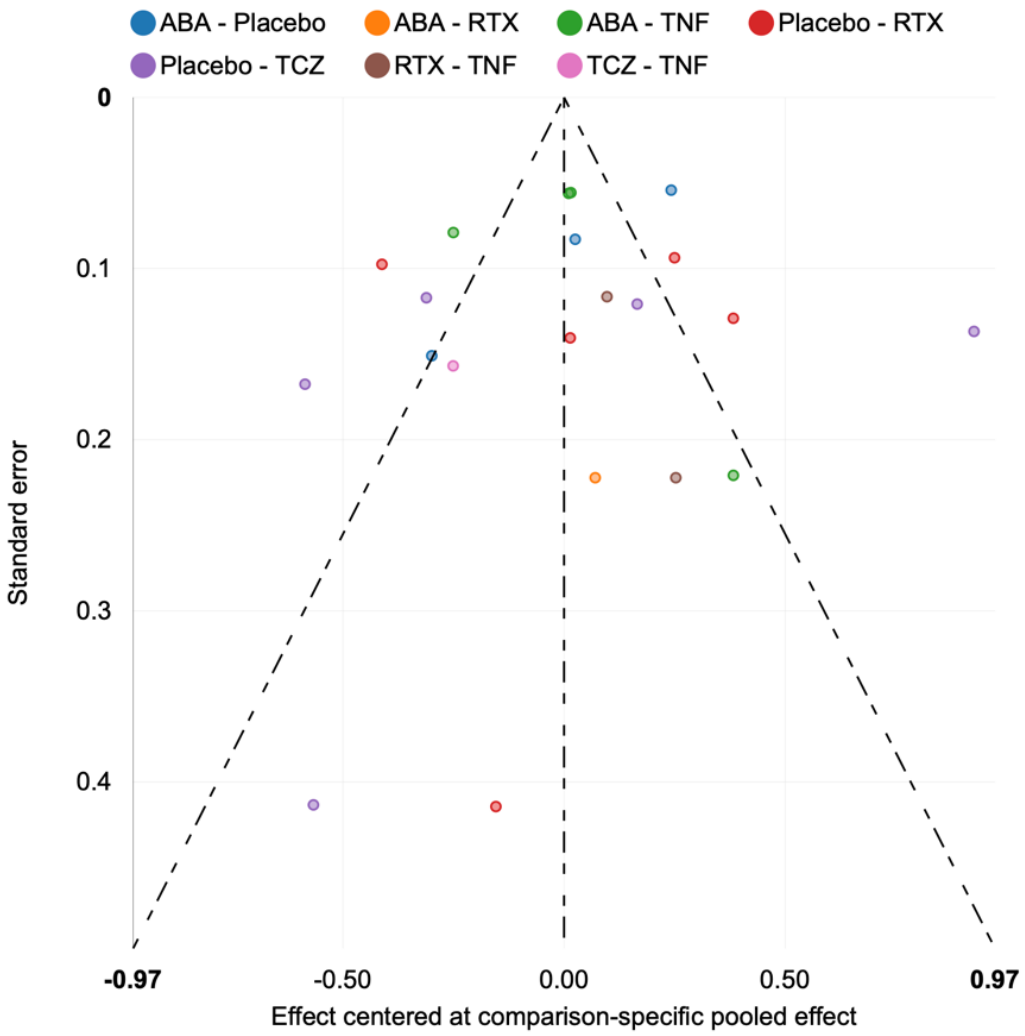
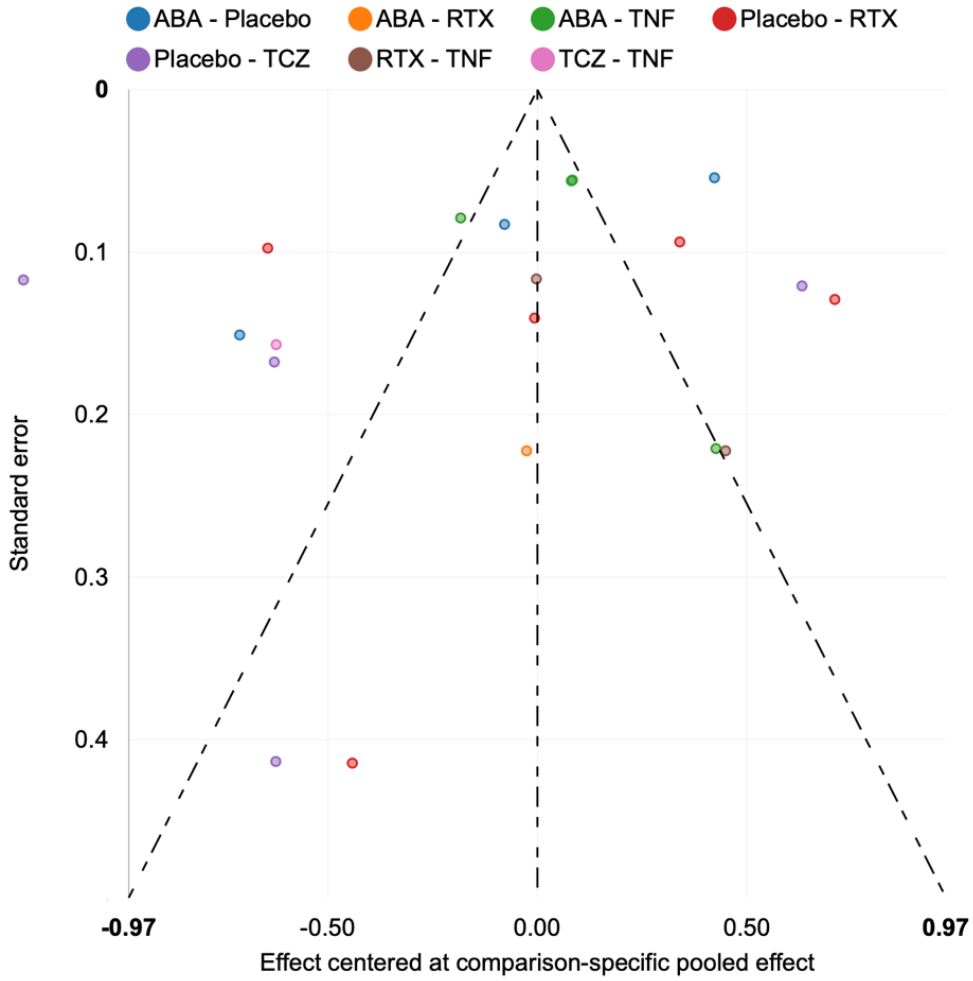


Figure C.3. Funnel plot for ACR 70 response



Supplementary file 8

Figure D.1: Forrest Plot ACR 70

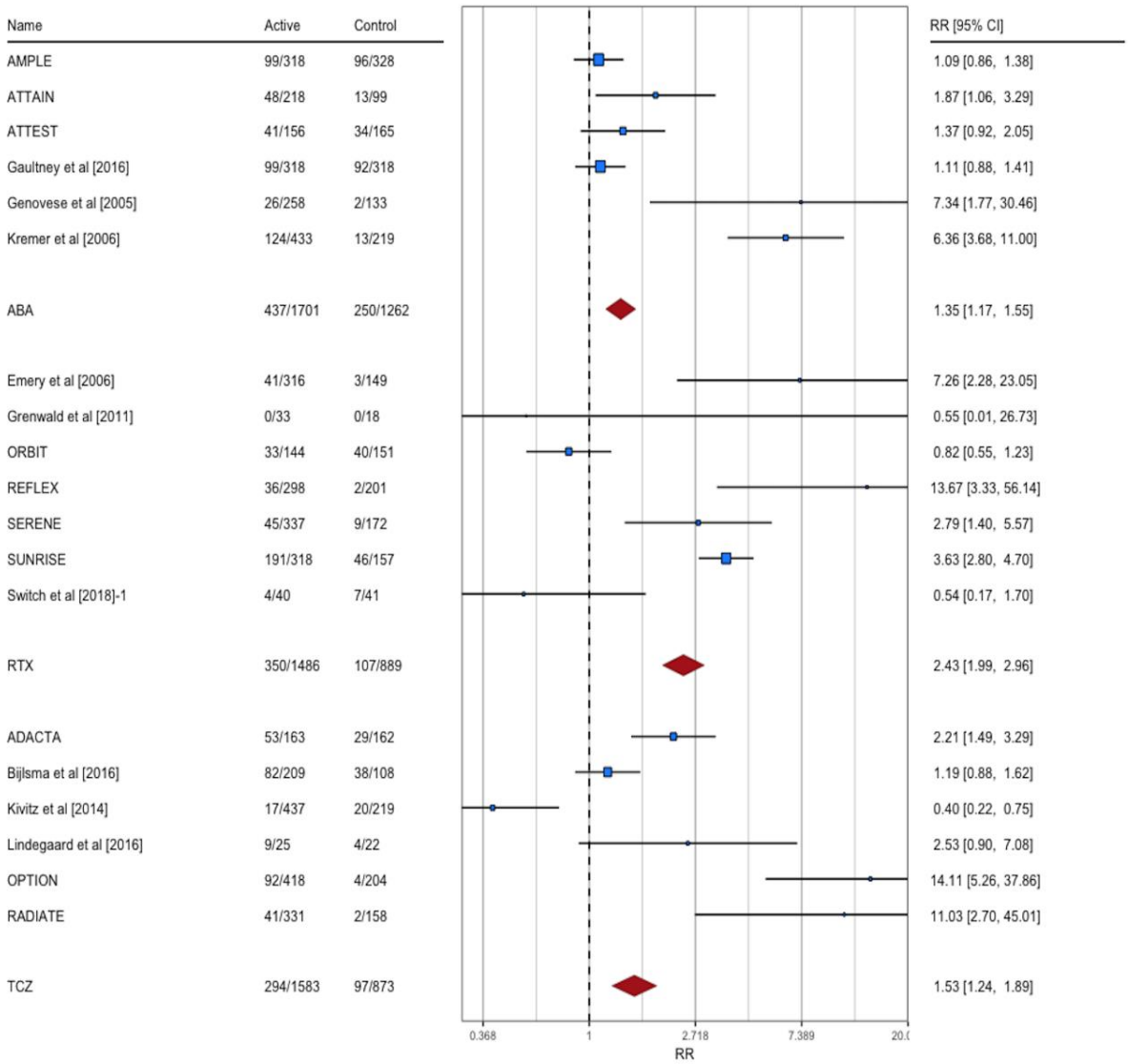


Figure D.2: Forrest Plot ACR 50

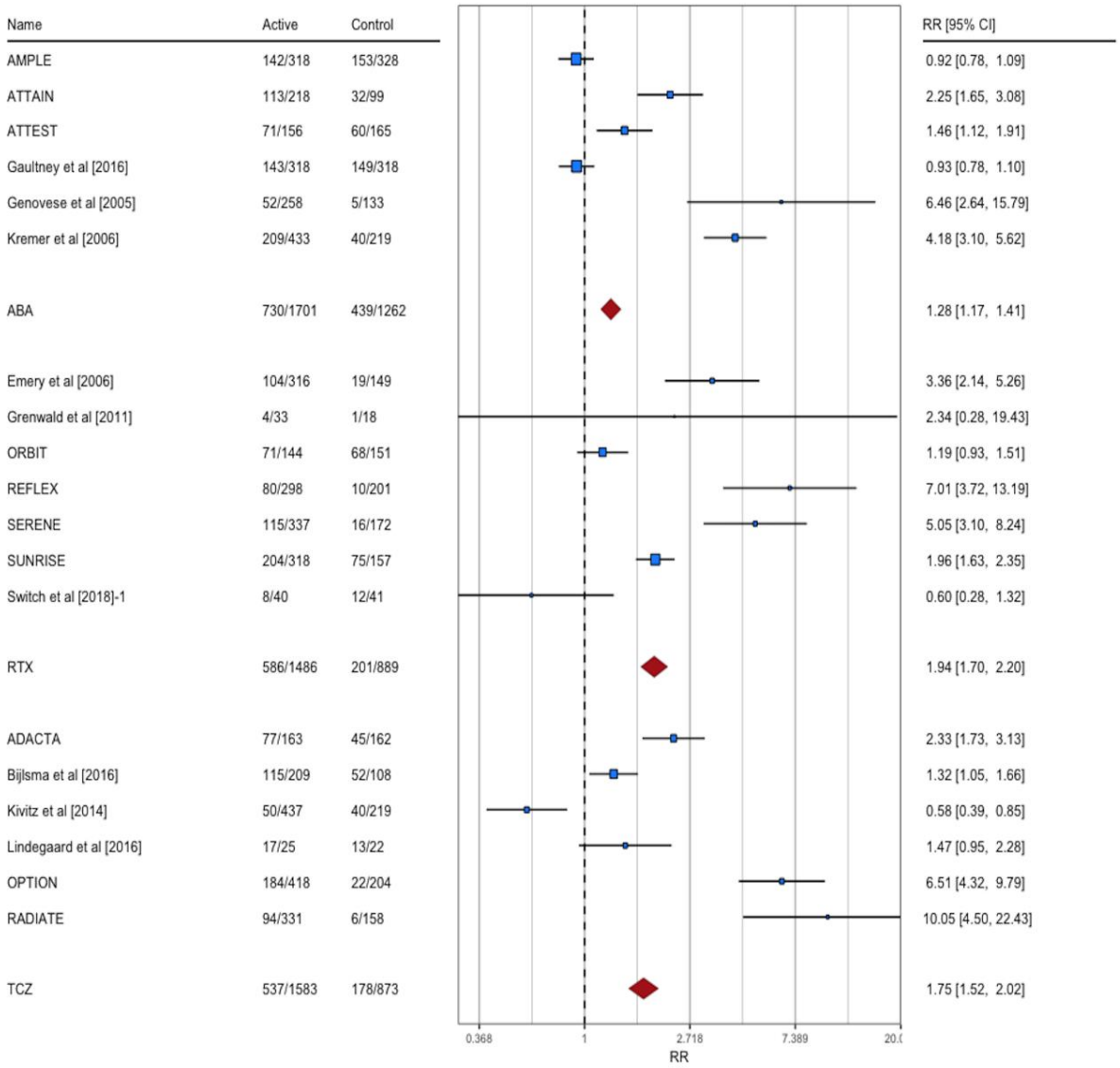
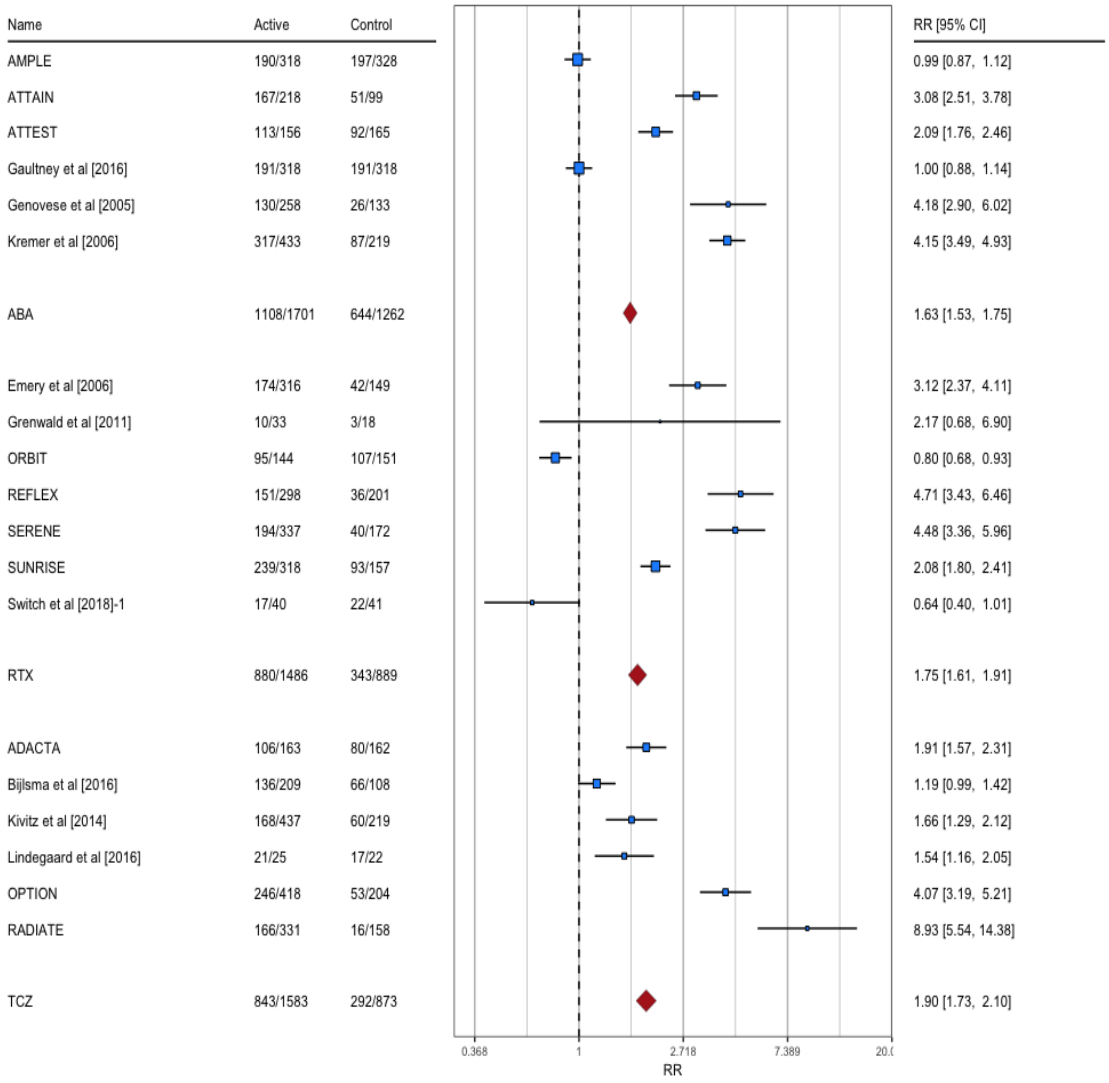


Figure D.3: Forrest Plot ACR 20



Supplementary file 9

Figure E.1 Mean HAQ and DAS28 vs ACR 70

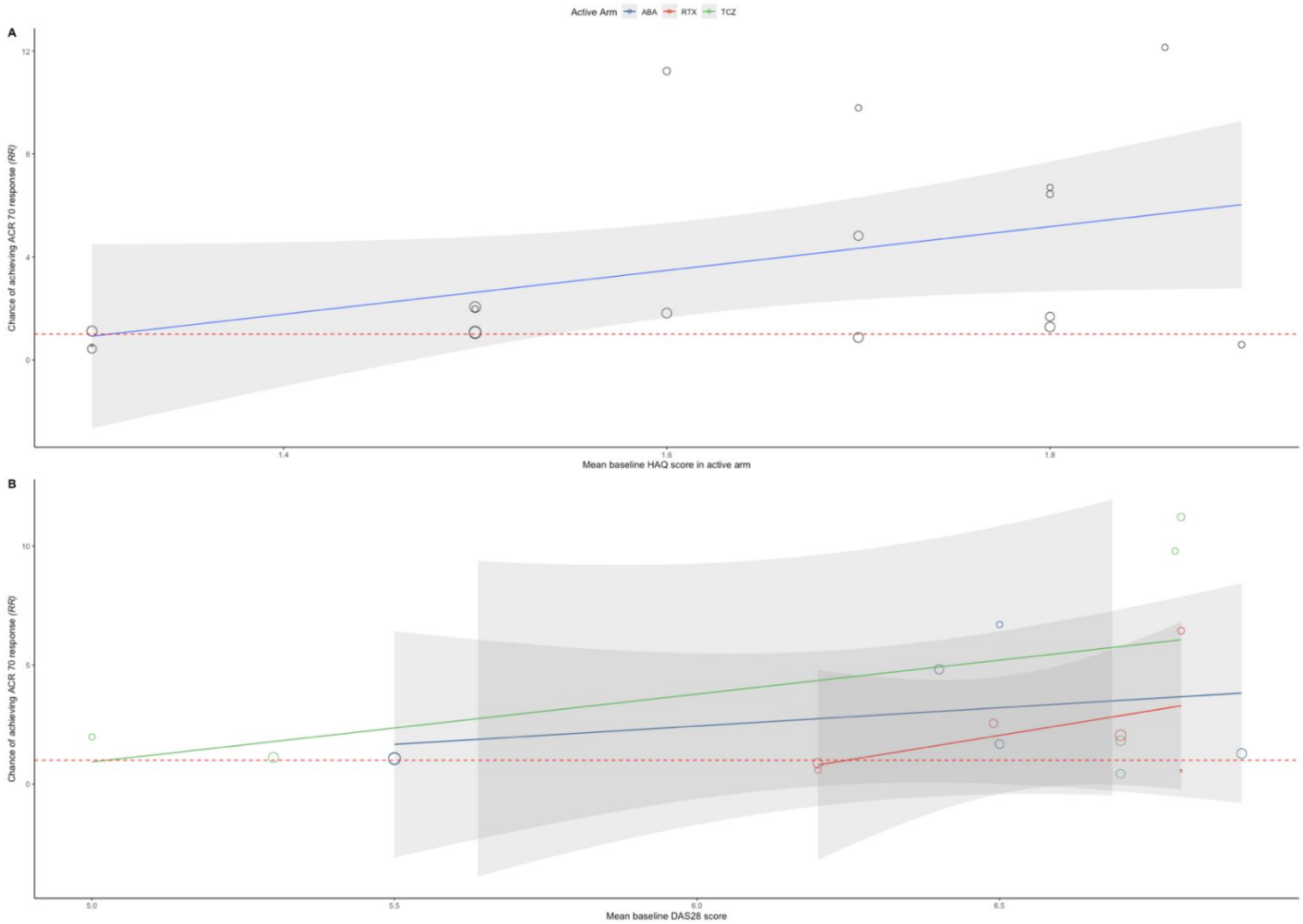


Figure E.2 Background antiTNF vs ACR 70

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