UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

FREQUÊNCIA DE ATIVIDADE MÍNIMA DE DOENÇA EM PACIENTES COM ARTRITE PSORIÁSICA: REVISÃO SISTEMÁTICA DA LITERATURA COM METANÁLISE

MARIELE ZARDIN MORAES

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"Que os vossos esforços desafiem as impossibilidades, lembrai-vos de que as grandes coisas do homem foram conquistadas do que parecia impossível"

Charles Chaplin

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RESUMO

Base teórica: A artrite psoriásica (AP) é doença inflamatória crônica, com manifestações heterogêneas. Recentemente, o critério de atividade mínima de doença (MDA - do inglês, *mínima ldisease activity*) tem sido proposto como alvo terapêutico. Acreditamos que a prevalência de pacientes que atinge MDA é diferente em ensaios clínicos randomizados (ECRs) e estudos de vida real.

Objetivo: estimar a freqüência de MDA em pacientes com AP em estudos de vida real e em ECRs, e por subtipo de tratamento (sintéticos versus biológico). Avaliar se há correlação entre MDA e SF36, e entre MDA e DAPSA, e analisar individualmente os componentes do MDA.

Métodos: foi realizada revisão sistemática da literatura no Pubmed, Embase, Cochrane e Lilacs, e busca nos anais de congressos EULAR, ACR, Conferência Mundial de Psoríase e AP, Congresso Internacional de Espondiloartrites e CBR. Os dados foram analisados por dois pesquisadores independentes, e as divergências resolvidas por consenso. Foi realizada metanálise de braço único para estimar freqüência de MDA em estudos de vida real e em ECRs, e por subtipo de tratamento. A heterogeneidade foi avaliada utilizando I^2. Foi avaliada a resposta de cada domínio de MDA ao longo do tempo, associação entre MDA e SF36, e correlação entre DAPSA e MDA.

Resultados:A freqüência de MDA em estudos de vida real foi de 37% (I^2=93%, IC 95% 36-38%), e em ECRs, 31% (I^2=78%, IC 95% 28-33%). Em pacientes em uso de DMARDs sintéticos (sDMARDs), 12% (I^2=0, IC 95% 8-18%), e, em biológicos (bDMARDs), 41% (I^2=92%, IC 95% 40-43%). Considerando apenas pacientes em uso de bDMARDs, em 6 meses de seguimento a freqüência de MDA foi de 32% (I^2=79%, IC 95% 26-39%) em ECRs, e de 30% (I^2=85%, IC 95% 21-41%) em estudos de vida real. Não houve correlação entre MDA e SF36 e nem associação entre DAPSA e MDA. Em média, houve melhora na maioria dos componentes do MDA aos 6 e 12 meses.

Conclusão: A freqüência de MDA em estudos de vida real foi diferente de ECRs, sugerindo uma maior freqüência em pacientes em uso de bDMARDs do que de sDMARDs. Considerando apenas pacientes em uso de bDMARDs, não houve diferença estatística na freqüência de MDA em ECRs e em estudos de vida real, em 6 meses de acompanhamento. Não houve correlação entre MDA e SF36 e nem associação entre DAPSA e MDA. Aos 6 e 12 meses, houve melhora na maioria dos componentes do MDA.

Palavras chave: MDA, minimal disease activity, atividade mínima de doença, artrite psoriásica.

ABSTRACT

Introduction: Psoriatic arthritis (PsA) is a chronic inflammatory disease with heterogeneous manifestations. Recently, minimal disease activity (MDA) has been proposed as a therapeutic target. We believe that the prevalence of MDA patients is different in randomized clinical trials (RCTs) and in real-life studies.

Objective: To estimate a frequency of MDA in patients with PsA in real-life studies and RCTs, and by subtype of treatment (synthetic versus biological). We are analyze whether there is correlation between MDA and SF36, MDA and DAPSA, and individually analyze the components of the MDA.

Methods:a systematic literature review was performed in Pubmed, Embase, Cochrane and Lilacs, and searched in the annals of EULAR, ACR, World Conference on Psoriasis and AP, International Congress on Spondylarthritis and CBR. The data were analyzed by two independent researchers, and the divergences resolved by consensus. Single-arm meta-analysis was performed to estimate MDA frequency in real-life studies and RCTs, and by treatment subtype. Heterogeneity was assessed using I^2. We evaluated the response of each MDA domain over time, association between MDA and SF36, and correlation between DAPSA and MDA.

Results: The frequency of MDA in real life studies was 37% (I^2 = 93%, CI 95% 36-38%), and in RCTs, 31% (I^2 = 78%, 95% CI 28-33%). In patients using synthetic DMARDs (sDMARDs), 12% (I^2 = 0, 95% CI 8-18%), and in biological (bDMARDs), 41% (I^2 = 92%, 95% CI 40-43%). Considering only patients on bDMARDs, the frequency of MDA was 32% (I^2 = 79%, 95%IC 26-39%) in RCTs and 30% (I^2 = 85%, 95% IC 21-41%) in real-life studies.There was no correlation between MDA and SF36 and no association between DAPSA and MDA. On average, there was improvement in most MDA components at 6 and 12 months.

Conclusion: The frequency of MDA in real-life studies was different from RCTs, suggesting a higher frequency in patients using bDMARDs than in sDMARDs. Considering only patients using bDMARDs, there was no statistical difference in the frequency of MDA in RCTs and in real-life studies at 6 months of follow-up.There was no correlation between MDA and SF36 and no association between DAPSA and MDA. At 6 and 12 months, there was improvement in most components of MDA.

Key words: MDA, minimal disease activity, psoriatic arthritis.

LISTA DE FIGURAS DA DISSERTAÇÃO

LISTA DE FIGURAS DO ARTIGO

LISTA DE TABELAS DA DISSERTAÇÃO

LISTA DE TABELAS DO ARTIGO

LISTA DE ABREVIATURAS E SIGLAS

ACR	*American College of Rheumatology*(Colégio Americano de Reumatologia)
AR	Artrite reumatóide
AP	Artrite Psoriásica
BASDAI	*Bath Ankylosing Spondylitis Disease Activity Index* (Índice de Atividade de Doença de Espondilite Anquilosante)
BASFI	*Bath Ankylosing Spondylitis Functional Index* (Índice de Função de Espondilite Anquilosante)
BCR	*Brazilian Congress of Rheumatology* (Congresso Brasileiro de Reumatologia)
bDMARDs	DMARDs biológicos
BSA	*Body Surface Area* (Área de Superfície Corporal)
CPDAI	*Composite Psoriatic Disease Activity Index* (Índice Composto de Atividade de Doença Psoriásica)
DAPSA	*Disease activity in Psoriatic Arthritis* (Atividade de Doença em Artrite Psoriásica)
DAS28	*Disease Activity Score 28 joints* (Escore de Atividade de Doença 28 articulações)
DMARD	*Disease-Modifying Antirheumatic Drugs* (Medicamentos Antirreumáticos Modificadores de Doença)
EA	Espondilite anquilosante
EULAR	*European League Against Rheumatism* (Liga Européia Contra o Reumatismo)
HAQ	*Health Assessment Questionnaire* (Questionário de Qualidade de Vida)
MDA	*Minimal Disease Activity* (Atividade Mínima de Doença)
OMERACT	*Outcome Measures in Rheumatology Clinical Trials* (Medidas de Desfecho em Estudos Clínicos Reumatológicos)
PASDAS	*Psoriatic Arthritis Disease Activity Score* (Escore de Atividade de Doença Artrite Psoriásica)

PASI	*Psoriasis Activity and Severity Index* (Índice de Atividade e Severidade de Psoríase)
PROs	*Patient-Reported Outcomes* (Desfechos relatados pelos Pacientes)
PsA	*Psoriatic Arthritis* (Artrite Psoriásica)
PsAQol	*PsA-Specific Quality of Life* (Qualidade de Vida Específico de Artrite Psoriásica)
RA	*Rheumatoid Arthritis* (ArtriteReumatóide)
RCT	*Randomized Controlled Trials* (Ensaios Clínicos Randomizados)
SD	*Standard Deviation* (Desvio Padrão)
sDMARDs	DMARDs sintéticos
SF36	*Medical Outcomes Short-Form Health Survey* (Forma Curta de Pesquisa de Desfechos Médicos de Saúde)
SF36 MCS	*SF36 Mental Component Summary* (Componente Sumário Mental do SF36)
SF36 PCS	*SF36 Physical Component Summary* (Componente Sumário Físico do SF36)
SJC	*Swollen Joint Count* (Contagem de Articulações Edemaciadas)
TJC	*Tender Joint Count* (Contagem de Articulações Dolorosas)
TNF	*Tumor Necrosis Factor* (Fator de Necrose Tumoral)

SUMÁRIO

1.INTRODUÇÃO

A artrite psoriásica (AP) é uma doença inflamatória crônica, que afeta cerca de 20-33% dos indivíduos com psoríase[1], e aproximadamente 133 em cada 100.000 indivíduos da população mundial, variando de acordo com idade e raça[2]. No Brasil, estima-se que aproximadamente 33% dos pacientes com psoríase apresentem AP [3]. Trata-se de uma doença heterogênea, que afeta tanto articulações periféricas como axiais, além da pele, podendo também desencadear uveíte, dactilite e entesites[4]. Além disso, como já citado anteriormente, é uma doença inflamatória, associada a dano articular[5] e progressão radiográfica[6], além de aumento do risco cardiovascular[7], obesidade, síndrome metabólica[8,9], e, consequentemente, ocasiona aumento da morbidade e mortalidade[10,11].

Em função de sua grande heterogeneidade, há uma dificuldade em realizar uma completa e ampla avaliação da atividade de doença na AP. Os instrumentos de avaliação de atividade usualmente utilizados são o DAS28 (do inglês, *Disease Activity Score* – Escore de Atividade de Doença)[12], quando há predominância de artrite periférica, e o BASDAI[13] (do inglês, *Bath Ankylosing Spondylitis Disease Activity Index* – Índice de Atividade de Doença de Espondilite Anquilosante), quando há predominância de sintomas axiais. Porém, esses instrumentos foram inicialmente desenvolvidos para avaliação de atividade na artrite reumatoide (AR) e na espondilite anquilosante (EA), respectivamente, e avaliam principalmente os sintomas articulares, carecendo de avaliação nos outros domínios da doença. Além disso, o DAS28 avalia apenas 28 articulações, o que torna esse instrumento incompleto mesmo na avaliação da doença articular na AP, já que o paciente com AP pode apresentar envolvimento de 68 articulações[14].

Dessa forma, tem se buscado, há muitos anos, o desenvolvimento de um instrumento que avalie a AP em todos os seus domínios. Atividade mínima de doença é definida pelo OMERACT (do inglês, *Outcome Measures in Rheumatology Clinical Trials*– Medidas de Desfecho em Estudos Clínicos Reumatológicos) como "um estado de atividade de doença considerado um alvo útil de tratamento por ambos paciente e médico, dadas as atuais possibilidades e limitações"[15]. Assim sendo, tem sido desenvolvidos diversos instrumentos de avaliação de atividade específicos para a AP, sendo os mais comuns o DAPSA (do inglês, *Disease Activity in Psoriatic Arthritis* - Atividade de Doença em Artrite Psoriásica)[16], o PASDAS (do inglês, *Psoriatic Arthritis Disease Activity Score* – Escore de Atividade de Doença de Artrite Psoriásica)[9], o CPDAI (do inglês, *Composite Psoriatic Disease Activity Index* – Índice Composto de Atividade de Doença Psoriásica)[17], e, mais recentemente, o MDA (do inglês, *Minimal Disease Activity* – Atividade Mínima de Doença)[18]. O DAPSA é um escore que avalia principalmente o acometimento articular da doença, englobando uma avaliação articular mais completa (68 articulações dolorosas e 66 articulações edemaciadas), porém ignora outros aspectos

da doença, como o acometimento da pele, de ênteses, e do esqueleto axial. Em contrapartida, o PASDAS e o CPDAI apresentam-se de uma forma mais completa, englobando, além da avaliação articular, a avaliação da qualidade de vida e presença de dactilite. Porém, o uso de múltiplos questionários e escalas torna inviável seu uso de rotina na prática clínica.

Foi nesse contexto, buscando-se uma forma de avaliação global da doença, factível de ser utilizada na prática clínica, que, em 2009, Coates e colaboradores apresentaram à comunidade científica o MDA: *Minimal Disease Activity* (atividade mínima de doença), que engloba 7 domínios da doença, que podem ser avaliados de forma simples e direta. O paciente é considerado em MDA quando apresenta 5 dos 7 critérios abaixo mencionados (tabela 1).

Tabela 1: Componentes do MDA.

Domínio	**Instrumento de avaliação**	**Critérios**
Dor articular	Contagem de articulações dolorosas (0-68)	≤ 1
Edema articular	Contagem de articulações edemaciadas (0-66)	≤1
Pele	PASI* (0-72)	≤ 1
Dor	VAS de dor (0-100mm)	≤ 15
Saúde global	VAS global (0-100mm)	≤ 20
Capacidade funcional	HAQ (0-3)	≤ 0,5
Ênteses	Número de ênteses dolorosas	≤ 1

PASI[19] = *Psoriasis Activity and Severity Index* (índice de atividade e severidade de psoríase); VAS[20] = *Visual Analogue Score* (escore visual analógico); HAQ[21] = *Health Assessment Questionnaire* (questionário de avaliação de saúde)*O PASI pode ser substituído pela área de superfície corporal ≤ 3%.

Recentemente, o MDA tem sido utilizado como alvo de tratamento da AP. O estudo TICOPA[22] analisou 206 pacientes com AP inicial (sintomas com duração menor que 24 meses), os quais foram randomizados em dois grupos de tratamento: um grupo com tratamento padrão (tratamento de acordo com seu médico, com reavaliação a cada 12 semanas, durante 48 semanas), e outro grupo recebendo tratamento intensivo baseado em metas, em inglês conhecido como *tight control*, em que o paciente era avaliado a cada 4 semanas, e, quando não estava em MDA, o tratamento era otimizado conforme um protocolo pré estabelecido. Em 48 semanas, o grupo de tratamento intensivo apresentou maiores taxas de ACR20[23], ACR50, ACR70[24] (melhora em 20, 50 e 70%, respectivamente, na resposta clínica segundo critérios do colégio americano de reumatologia) e PASI20, PASI75 e PASI 90, porém sem diferenças na progressão radiográfica. Além disso, o grupo tight control apresentou melhores índices de desfechos relatados pelo paciente (*Patient-Reported Outcomes* – PROs), como o

BASDAI**,** que avaliasintomasaxiais, fadiga, sintomas periféricos e entesites, melhores escores nas ferramentas que avaliam capacidade funcional, como o BASFI[25] (do inglês, *Bath Ankylosing Spondylitis Functional Index* – Índice Funcional de Espondilite Anquilosante) **e** HAQ, assim como melhor qualidade de vida avaliada pelo PsAQol (do inglês, *PsA-Specific Quality of Life* – Qualidade de Vida Específico de Artrite Psoriásica)[26]. Em contrapartida, no grupo *tight control* houve um maior uso de terapia biológica, e um maior número de eventos adversos. Além disso, houve um maior gasto no tratamento no grupo *tight control* (aproximadamente duas vezes mais caro) do que no grupo com tratamento padrão.

Outro estudo de grande relevância, em que o MDA foi utilizado, é o GO-REVEAL[27], em que 396 pacientes foram randomizados em 2 grupos (placebo x golimumabe) até a semana 24, quando então todos os pacientes passaram a receber golimumabe, e seguiram em uma fase aberta até completarem 5 anos de tratamento. Ao longo desses 5 anos, a progressão radiográfica foi significativamente menor nos pacientes que estavam em MDA, sendo inversamente proporcional ao tempo em que esses pacientes permaneciam em MDA. Ademais, a progressão radiográfica foi menor naqueles pacientes que atingiam MDA baseados em 6 dos 7 e em 7 dos 7 componentes[28].

A prevalência de pacientes com AP que fecha critérios para MDA em ensaios clínicos varia de 14 até 52%, conforme publicação recente[29].Porém, sabemos que os pacientes, ao serem recrutados para participarem de ensaios clínicos, em geral têm menos comorbidades e maior atividade de doença, e apresentam um controle mais estrito, recebendo a medicação de forma controlada, com melhores índices de aderência[30]. Na vida real, em que os pacientes sofrem diversas dificuldades, tanto na aquisição das medicações, quanto nos fatores que proporcionam um acompanhamento adequado, ainda permanecem dúvidas se esses resultados são reprodutíveis.

2. REVISÃO DA LITERATURA

2.1 Estratégias para localizar e selecionar as informações

Uma extensa pesquisa bibliográfica foi realizada em abril de 2017 no Pubmed, Embase, Cochrane Library e Lilacs, sem limites ou filtros de qualquer tipo. As seguintes estratégias de pesquisa foram utilizadas:

Pubmed e Cochrane:

((“minimal disease activity” OR “minimal disease activities” OR “MDA”)) AND ("Arthritis, Psoriatic"[Mesh] OR “Psoriasis, Arthritic” OR “Arthritic Psoriasis” OR “Psoriatic Arthritis” OR “Psoriasis Arthropathica” OR “Psoriatic Arthropathy” OR “Arthropathies, Psoriatic” OR “Arthropathy, Psoriatic” OR “Psoriatic Arthropathies” OR “Spondylarthropathies"[Mesh] OR “Marie-Strumpell Spondylitis” OR “Marie Strumpell Spondylitis” OR “Spondylitis, Marie-Strumpell” OR “Spondyloarthropathy” OR “Spondyloarthropathies” OR “Bechterew Syndrome” OR “Syndrome, Bechterew” OR “Spondylarthropathy” OR "Spondylarthritis"[Mesh] OR “Spondylarthritides” OR “Spinal Arthritis” OR “Spinal Arthritides” OR “Arthritis, Spinal”)

Embase:
'minimal disease activity' OR 'minimal disease activities' OR 'MDA'
AND
'psoriatic arthritis'/exp OR 'psoriatic arthritis' OR 'alibertbazin disease' OR 'arthritis psoriatica' OR 'arthritis, psoriatic' OR 'arthritis, psoriasis' OR 'arthritis, psoriatic' OR 'arthropathic psoriasis' OR 'arthropathy, psoriatic' OR 'disease, alibertbazin' OR 'polyarthritis, psoriatic' OR 'psoriasis arthropathica' OR 'psoriasis pustulosaarthropathica' OR 'psoriasis, arthritis' OR 'psoriatic arthropathy' OR 'psoriatic polyarthritis' OR 'psoriatic rheumatism' OR 'psoriatic rheumatoid arthritis' OR 'rheumatoid arthritis, psoriatic'

Lilacs: Minimal AND disease AND activity AND psoriatic arthritis

Uma busca ativa por resumos apresentados nos principais Congressos de Reumatologia de 2009 a 2017 foi realizada e incluiu: o Congresso Anual Europeu de Reumatologia da Liga Europeia Contra o Reumatismo (EULAR), a Reunião Anual do Colégio Americano de Reumatologia (ACR), a Conferência Mundial de Psoríase e Artrite Psoriásica, Congresso Internacional de Espondiloartrites e Congresso Brasileiro de Reumatologia (CBR).

Um total de 405 artigos foram identificados a partir das bases de dados; 274 foram excluídos por título e resumo, e 96 estudos foram excluídos após análise do texto completo. Dez resumos foram identificados nos anais de congressos de reumatologia;

45 artigos elegíveis foram incluídos na análise. O fluxograma do processo de seleção dos estudos está representado na Figura 1.

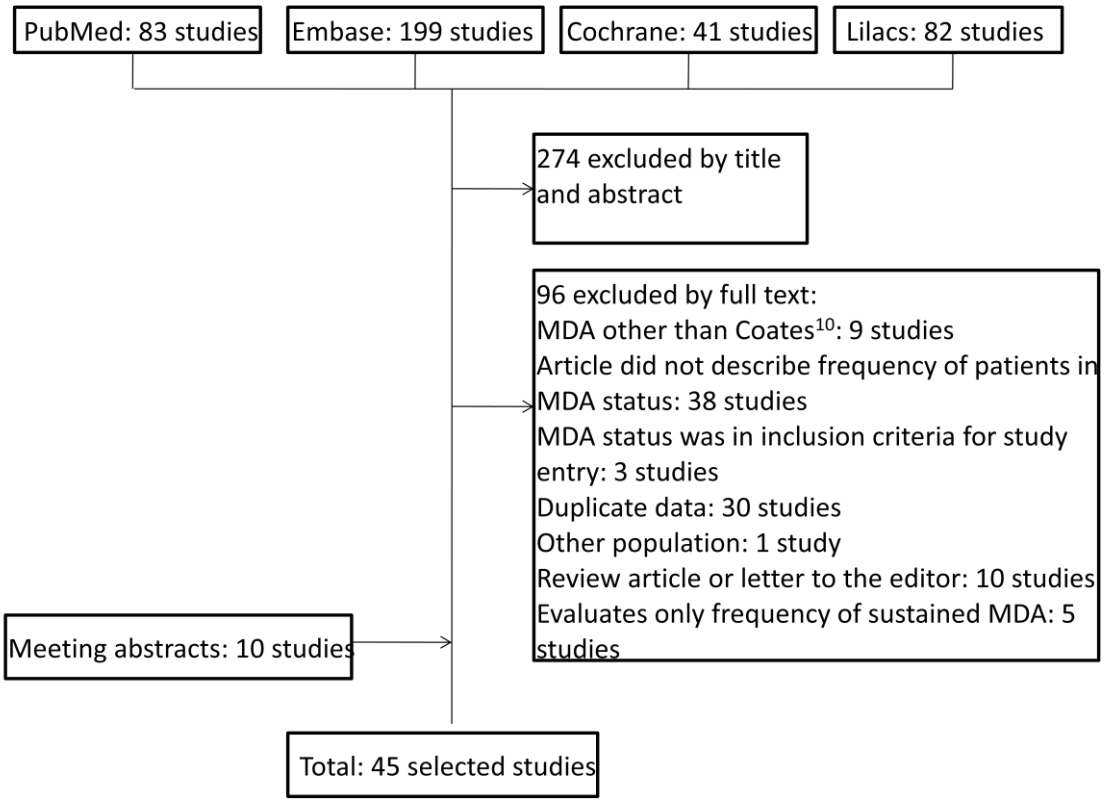

Figura 1: Fluxograma demonstrando a seleção dos artigos.

3. MARCO CONCEITUAL

A figura 2 representa o marco conceitual do estudo.

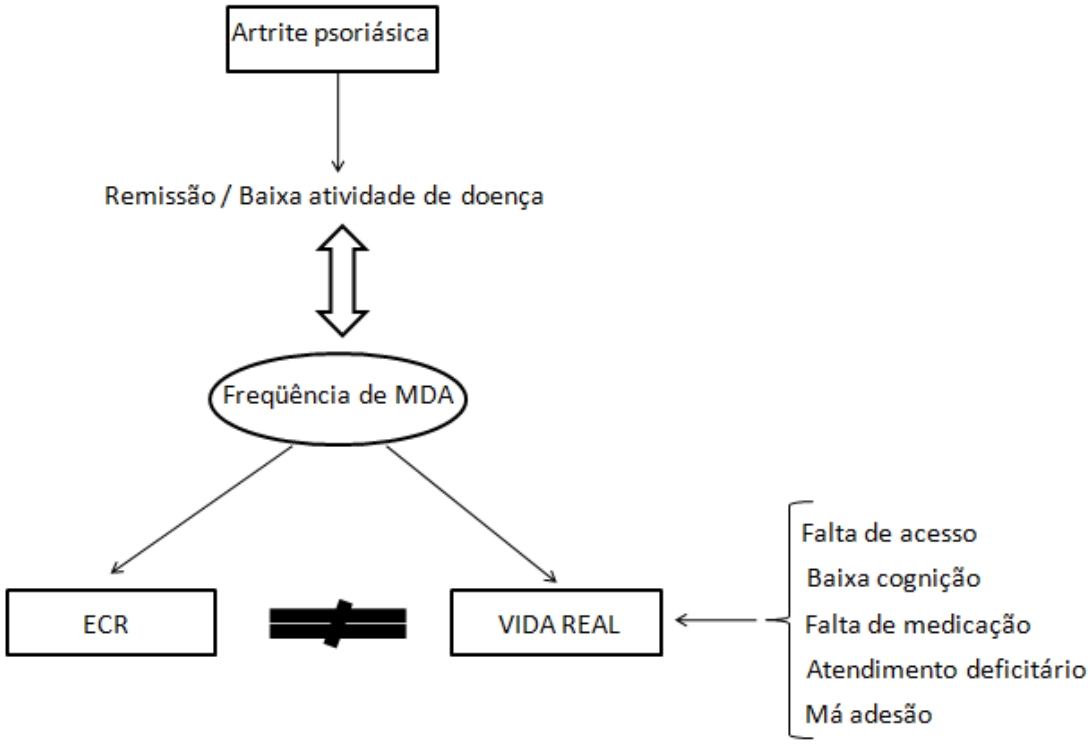

Figura 2: Marco conceitual

4. JUSTIFICATIVA

A AP é uma doença inflamatória sistêmica, que causa deformidades e incapacidade funcional a longo prazo, aumentando morbimortalidade dos pacientes[10]. À semelhança da AR, que é outra forma de artrite erosiva[31], há evidências, principalmente através de resultados de ensaios clínicos randomizados, que o tratamento baseado em metas na artrite psoriásica, e consequentemente, o fato de se atingir e manter MDA, melhora alguns desfechos clínicos a longo prazo, como função física, qualidade de vida, e diminui progressão radiográfica, porém ter MDA como alvo terapêutico pode acarretar em mais despesas para o tratamento, e um maior número de eventos adversos[32,33].

Até o momento, as evidências mais robustas sobre esse escore provêm de ECR, tendo poucas publicações em vida real. Muitas vezes, na vida real, o acesso às medicações e ao atendimento médico especializado é dificultado, assim como, quando há disponibilidade desses recursos, com grande freqüência, há abandono ou má adesão ao tratamento, seja por falta de compreensão, dificuldades financeiras, benefícios secundários, entre outras causas, o que, provavelmente, torna reduzida a chance de se atingir MDA nesse cenário. Buscamos, com esse trabalho, avaliar a freqüência de MDA em estudos de vida real, comparando também com a freqüência em ECR, e de acordo com o tratamento; avaliar o que já foi publicado sobre MDA em estudos de vida real, determinando assim a viabilidade desse escore na prática clínica, sua associação com outros desfechos, como função e qualidade de vida, se é factível de ser realizado na vida real, e se o fato de atingir ou não MDA traz benefícios para o paciente, oferecendo perspectivas na melhora do tratamento na AP.

5. OBJETIVOS

5.1 Objetivo primário

Avaliar a frequência de pacientes com artrite psoriásicaque atingem MDA em estudos observacionais (de vida real).

5.2 Objetivos secundários

5.2.1 Estimar as respostas de cada domínio do MDA: número de articulações dolorosas e edemaciadas, PASI, VAS global e de dor, HAQ, e número de enteses dolorosas.

5.2.2 Estudar a associação entre MDA e qualidade de vida.

5.2.3 Analisar as frequências de MDA de acordo com o tratamento realizado (tratamento biológico *versus*sintético).

5.2.4 Comparar a frequência de pacientes que atingem MDA em estudos de vida real e em ensaios clínicos randomizados.

5.2.5 Calcular a acurácia de MDA na identificação de remissão de artrite psoriásica.

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7. ARTIGO EM INGLÊS

FREQUENCY OF MINIMAL DISEASE ACTIVITY IN PATIENTS WITH PSORIATIC ARTHRITIS – SYSTEMATIC LITERATURE REVIEW WITH META-ANALYSIS

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ABSTRACT

Introduction: Psoriatic arthritis (PsA) is a chronic inflammatory disease with heterogeneous manifestations. Recently, minimal disease activity (MDA) has been proposed as a therapeutic target. We believe that the prevalence of MDA patients is different in randomized clinical trials (RCTs) and in real-life studies.

Objective: To estimate a frequency of MDA in patients with PsA in real-life studies and RCTs, and by subtype of treatment (synthetic versus biological). We are analyze whether there is correlation between MDA and SF36, MDA and DAPSA, and individually analyze the components of the MDA.

Methods:a systematic literature review was performed in Pubmed, Embase, Cochrane and Lilacs, and searched in the annals of EULAR, ACR, World Conference on Psoriasis and AP, International Congress on Spondylarthritis and CBR. The data were analyzed by two independent researchers, and the divergences resolved by consensus. Single-arm meta-analysis was performed to estimate MDA frequency in real-life studies and RCTs, and by treatment subtype. Heterogeneity was assessed using I^2. We evaluated the response of each MDA domain over time, association between MDA and SF36, and correlation between DAPSA and MDA.

Results: The frequency of MDA in real life studies was 37% (I^2 = 93%, CI 95% 36-38%), and in RCTs, 31% (I^2 = 78%, 95% CI 28-33%). In patients using synthetic DMARDs (sDMARDs), 12% (I^2 = 0, 95% CI 8-18%), and in biological (bDMARDs), 41% (I^2 = 92%, 95% CI 40-43%). Considering only patients on bDMARDs, the frequency of MDA was 32% (I^2 = 79%, 95%IC 26-39%) in RCTs and 30% (I^2 = 85%, 95% IC 21-41%) in real-life studies.There was no correlation between MDA and SF36 and no association between DAPSA and MDA. On average, there was improvement in most MDA components at 6 and 12 months.

Conclusion: The frequency of MDA in real-life studies was different from RCTs, suggesting a higher frequency in patients using bDMARDs than in sDMARDs. Considering only patients using bDMARDs, there was no statistical difference in the frequency of MDA in RCTs and in real-life studies at 6 months of follow-up.There was no correlation between MDA and SF36 and no association between DAPSA and MDA. At 6 and 12 months, there was improvement in most components of MDA.

Key words: MDA, minimal disease activity, psoriatic arthritis.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease that affects about 20-33% of individuals with psoriasis[1], and approximately 133 in every 100,000 individuals of the world population, varying according to age and race[2]. PsA has heterogeneous manifestations, affecting peripheral and axial joints, skin, nails, and enthesis[34].

The use of disease activity scores in rheumatoid arthritis (RA) is well established and it is the basis of the treat-to-target approach[35]. However, the clinical evaluation of PsA is much more complex and includes numerous domains, being difficult to establish a target.The minimal disease activity (MDA) criteria has been recommended as a therapeutic target in PsA[36,37]. Patients are classified as achieving MDA if they fulfill 5 out of 7 outcome measures: tender joint count (TJC) ≤1; swollen joint count (SJC) ≤1; psoriasis activity and severity index (PASI) ≤1[19] or body surface area (BSA) ≤3; patient pain visual analog scale (pain VAS) score≤15; patient global disease activity (global VAS[20]) score ≤20; Health Assessment Questionnaire (HAQ) score ≤0.5[21]; and tender entheseal points ≤1[18].

MDA has been assessed in several trials and its frequency varies according to the study design, drug and time of evaluation: the frequency of MDA in Randomized Controlled Trials (RCT) varies between 24-52% with tumor necrosis factor (TNF) inhibitor therapy and 14-41% with secukinumab; and between 40-64% in observational studies[29].

Participants of RCTs usually present higher levels of disease activity, fewer comorbidities, and better adherence rates to therapy than patients analyzed in observational studies[30]. In real life, several factors such as poor adherence and restricted access to drugs preclude the achievement of the MDA status. The aim of the current investigation is to analyze the frequency of PsA patients achieving MDA status in real-life studies. Secondary objectives are the frequency of MDA by type of study (observational versus RCT) and by type of treatment i.e., synthetic versus biological DMARD (Disease-Modifying Antirheumatic Drugs) – sDMARDs versus bDMARDs.

METHODS

The present study is a systematic review with meta-analysis of observational and interventional studies reporting MDA in PsA patients.

Study protocol

The protocol for this systematic review is found in the PROSPERO record (Internationalprospectiveregisterofsystematicreviews).CRD42016050502. It can be accessed in:http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016050502.

Search strategy

An extensive literature search was performed on April 2017 in Pubmed, Embase, Cochrane and Lilacs with no limits or filters. The following search strategies were used:

Pubmed and Cochrane:
((“minimal disease activity” OR “minimal disease activities” OR “MDA”)) AND ("Arthritis, Psoriatic"[Mesh] OR “Psoriasis, Arthritic” OR “Arthritic Psoriasis” OR “Psoriatic Arthritis” OR “Psoriasis Arthropathica” OR “Psoriatic Arthropathy” OR “Arthropathies, Psoriatic” OR “Arthropathy, Psoriatic” OR “Psoriatic Arthropathies” OR “Spondylarthropathies"[Mesh] OR “Marie-Strumpell Spondylitis” OR “Marie Strumpell Spondylitis” OR “Spondylitis, Marie-Strumpell” OR “Spondyloarthropathy” OR “Spondyloarthropathies” OR “Bechterew Syndrome” OR “Syndrome, Bechterew” OR “Spondylarthropathy” OR "Spondylarthritis"[Mesh] OR “Spondylarthritides” OR “Spinal Arthritis” OR “Spinal Arthritides” OR “Arthritis, Spinal”)

Embase:
'minimal disease activity' OR 'minimal disease activities' OR 'MDA'
AND
'psoriatic arthritis'/exp OR 'psoriatic arthritis' OR 'alibertbazin disease' OR 'arthritis psoriatica' OR 'arthritis, psoriatic' OR 'arthritis, psoriasis' OR 'arthritis, psoriatic' OR 'arthropathic psoriasis' OR 'arthropathy, psoriatic' OR 'disease, alibertbazin' OR 'polyarthritis, psoriatic' OR 'psoriasis arthropathica' OR 'psoriasis pustulosaarthropathica' OR 'psoriasis, arthritis' OR 'psoriatic arthropathy' OR 'psoriatic polyarthritis' OR 'psoriatic rheumatism' OR 'psoriatic rheumatoid arthritis' OR 'rheumatoid arthritis, psoriatic'

Lilacs: Minimal AND disease AND activity AND psoriatic arthritis

An active search for abstracts presented in the main Rheumatology Congress from 2009 to 2017 was carried out and included: the European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology, the American College of Rheumatology (ACR) Annual Meeting, the World Psoriasis and Psoriatic Arthritis Conference, the International Congress of Spondyloarthropathies, and the Brazilian Congress of Rheumatology (BCR).

Inclusion criteria. Original studies reporting the frequency (prevalence or incidence) of MDA in adult patients with PsA. Articles were included and there was no limit for data of publication or language.

Exclusion criteria.i) duplicates (in case of duplicates, the most complete publication was included); ii) review articles, letter to editor, case reports; iii) articles not describing MDA according to Coates[18], e.g., studies that evaluated number of

swollen joints other than 66 and tender joints other than 68, studies that didn't evaluate enthesitis, etc.; iv) articles reporting only the prevalence of sustained MDA.

Selection of studies. Two reviewers (MM and CK) independently selected the articles by title and abstract. In the next step, two researchers (MM and PP), independently selected the articles based on full text. The discordances were solved by consensus.

Data collection. The following data were extracted: first author, year of publication, country where the study was conducted, duration of the study, type of publication (original article versus abstract presented in congress), study design (RCT, cohort or cross-sectional), total number of patients included in the study, total number and relative frequency of women included in the study, mean age of the population, PsA duration, number of comorbidities, type of treatment, time of evaluation, number and perceptual of participants achieving the MDA status, mean and standard deviation (SD) of each component of MDA criteria; mean (±SD) Disease Activity in Psoriatic Arthritis (DAPSA) scores, mean (±SD) Medical Outcomes Short-Form Health Survey (SF36) Physical and Mental Component Summary scores (SF36 PCS and SF36 MCS, respectively). These data were independently extracted from articles by two reviewers (MM e CS), and the discordances were solved by consensus.

Risk of bias. Studies included in the analysis were assessed for risk of bias by two independent researchers (MM and LH); disagreements were solved by consensus. The instrument adopted for evaluation of bias differed according to study design: the Cochrane evaluation tool for RCTs, the New-Castle Ottawa Scale for cohort studies; the adapted New-Castle Ottawa Scale for cross sectional studies (this scale was adapted by PA Modesti et al. Panethnic differences in blood pressure in europe: a systematic review and meta-analysis). All studies fulfilling the inclusion criteria were included in the analysis regardless of their risk of bias.

Statistical analyses. For analysis of the primary outcome, a single-arm meta-analysis was performed, grouping both cohort and cross-sectional studies. For the cross sectional studies, zero time was considered, and for the cohort studies, the final follow-up time of each study was considered. Single arm meta-analysis was also performed for time subgroups in cohort studies, i.e. zero time, 3-4 months, 6-8 months, 12-13 months, and 24-60 months follow-up.For the observational studies, single arm meta-analysis was also performed for each treatment subgroup (biologics DMARDs versus other types of treatment, i.e., synthetic DMARDs, non-steroidal anti-inflammatory drugs).

Single-arm meta-analysis was also performed to estimate the frequency of MDA in randomized clinical trials, considering maximum follow-up time. Single-arm meta-analyses for each treatment subgroup (sDMARDs monotherapy, bDMARDs monotherapy, combined DMARDs + bDMARDs and unspecified treatment), and two-arm meta-analysis comparing treatment types (interventional therapy versus placebo) were also performed. In addition, a single-arm meta-analysis was performed to analyze the frequency of MDA in patients using bDMARDs in real-life studies versus RCTs at 6 months follow-up.

The results of the meta-analysis were represented by forest plots. I^2index was used to assess the heterogeneity between studies.When relevant heterogeneity was found (I^2index greater than 50%[38]), the results from the random effects model were showed, and, in cases where $I^2$is less than 50%, the fixed effects model was used. For

the evaluation of the components of the MDA, a radar chart was performed with the average percentage variation of all components at 6 and 12 months compared to baseline, in studies where such data were available (cohort study or RCT). To assess the association of MDA with quality of life, a scatter plot was constructed with the percentage of patients in MDA on the X axis, and the values of SF36 on the Y axis. A graph was made for SF36 MCS and another one for SF36 PCS.And finally, to study association between MDA and DAPSA, a 2x2 table was created with MDA (yes / no) versus DAPSA (remission or low activity versus moderate or high activity). The correlation and agreement between percentages of remission and low disease activity of the two scores were then calculated.

RESULTS

A total of 405 articles were identified from databases, 274 were excluded by title and abstract and 96 studies were excluded after full text analysis. Ten abstracts were identified in the annals of rheumatology meetings; 45 eligible articles were included in the analysis. The flow chart of study selection process is represented in Figure 1.

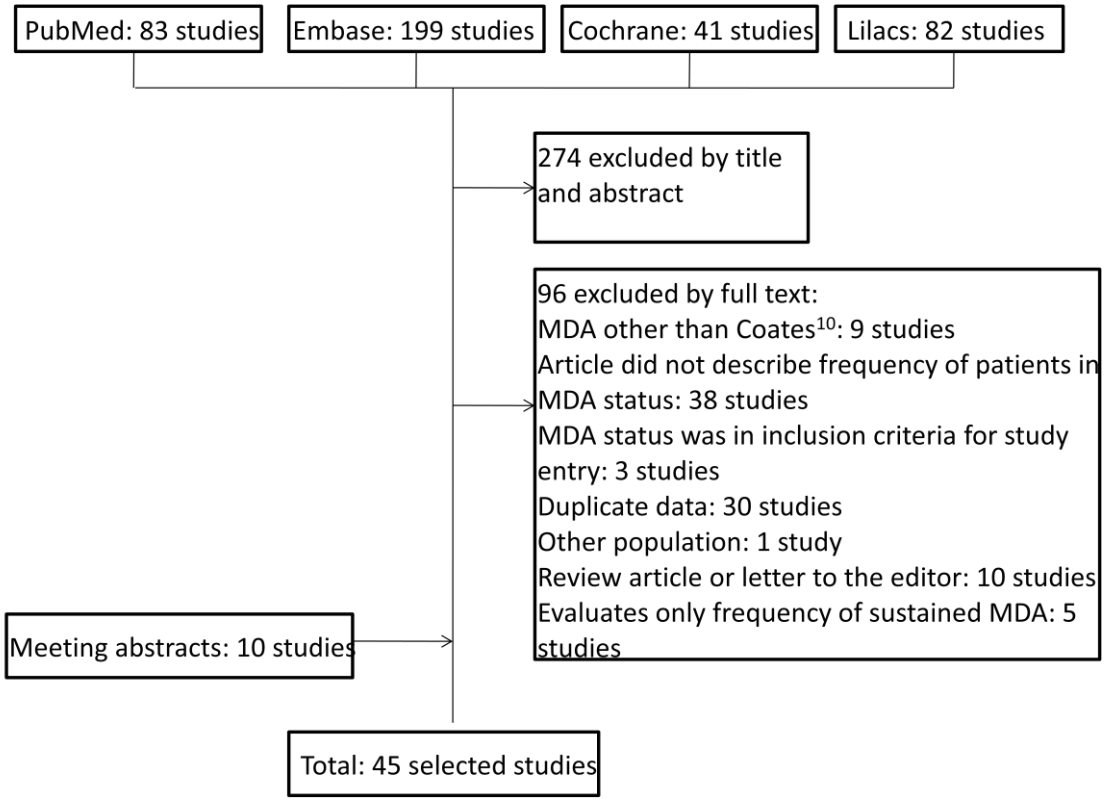

Figure 1: Flow chart showing the selection of studies for inclusion in the meta-analysis.

The 45 selected studies included 12,469 patients, mean age (SD) 51.0 (±3.3) years, most part were men (N= 6,386, 51.2%) with a mean PsA duration (SD) 8.1 (±3.6) years.Of the 45 selected studies, 39 (86.7%) were real-life and only 6 studies(13.3%) were RCTs. The 45 studies included in the analysis are shown in Table 1, and the characteristics of these studies are shown in table 2.

Table 1: Selected studies

AUTHOR	YEAR	COUNTRY	FOLLOW-UP TIME (MONTHS)	PUBLICATION TYPE	STUDY DESIGN
Felquer MLA, 2014[34]	2014	Argentina	0	Original article	Cross-sectional
Mease P, 2017[39]	2017	USA	36	Meeting abstract	Cohort
Tsuji S, 2015[40]	2015	Japan	13	Meeting abstract	Cohort
Queiro R, 2016[41]	2016	Spain	0	Meeting abstract	Cross-sectional
Elmamoun M, 2016[42]	2016	Ireland	0	Meeting abstract	Cohort
Deodhar A, 2017[43]	2017	USA/ Switzerland	6	Meeting abstract	RCT
Di Minno MND, 2014[44]	2014	Italy	6	Original article	Cohort
Rahman P, 2015[45]	2015	Canada	12	Meeting abstract	Cohort
Mease PJ, 2016[46]	2016	USA	0	Meeting abstract	Cross-sectional
Behrens F, 2016[47]	2016	Germany	24	Meeting abstract	Cohort
Zaffarana C, 2016[48]	2016	Argentina	0	Meeting abstract	Cross-sectional
Felquer MLA, 2013[49]	2013	Argentina	3	Meeting abstract	Cohort
Got M, 2016[50]	2016	Canada	0	Meeting abstract	Cross-sectional
Brikman S, 2016[51]	2016	Israel	0	Original article	Cross-sectional
Coates LC, 2010 (post hoc IMPACT 2)[18]	2010	United Kingdom	6	Original article	RCT
Coates LC, 2016[33]	2016	United Kingdom	0	Original article	Cross-sectional
Coates LC, 2016 (post hoc SPIRIT-P1)[52]	2016	United Kingdom	6	Meeting abstract	RCT

Costa L, 2014[53]	2014	Italy	24	Original article	Cohort
Geijer M, 2015[54]	2015	Sweden	60	Original article	Cohort
Haddad A, 2014[55]	2014	Canada	0	Original article	Cross-sectional
Husic R, 2014[56]	2014	Austria	0	Original article	Cross-sectional
Iervolino S, 2012[57]	2012	Italy	3	Original article	Cohort
Janta I, 2015[58]	2015	Spain	0	Original article	Cross-sectional
Kalyoncu U, 2016[59]	2016	Turkey	0	Original article	Cross-sectional
Kavanaugh A, 2016[33]	2016	Multicentric	6	Original article	RCT
Kerr G, 2014[60]	2014	USA	0	Original article	Cross-sectional
Leung YY, 2016[61]	2016	Singapore	0	Original article	Cross-sectional
Lubrano E, 2015[62]	2015	Italy	12	Original article	Cohort
Lubrano E, 2016[63]	2016	Italy	12	Original article	Cohort
Marin J, 2016[64]	2016	Argentina	0	Original article	Cross-sectional
Michelsen B, 2017[65]	2017	USA/Norway	0	Original article	Cross-sectional
Pappone N, 2015[66]	2015	Italy/Israel	0	Original article	Cross-sectional
Perrotta F, 2016[67]	2016	Italy	12	Original article	Cohort
Sheane BJ etal[68]	2016	Canada	6	Original article	Cohort
Theander E, 2014[69]	2014	Sweden	60	Original article	Cohort
Mease PJ, 2015[70]	2015	USA	0	Meeting abstract	Cross-sectional
Mease PJ, Karki C, 2015[71]	2015	USA	0	Meeting abstract	Cross-sectional
Luime J, 2015[72]	2015	Netherlands	6	Meeting abstract	Cohort
Szentpetery A, 2016[73]	2016	Ireland	0	Meeting abstract	Cross-sectional

Saldanha C, Zardin M, 2016[74]	2016	Brazil	0	Meeting abstract	Cross-sectional
Mease PJ, 2016[75]	2016	Multicentric	4	Meeting abstract	RCT
Perrota FM, 2017[76]	2017	Italy	0	Meeting abstract	Cross-sectional
Coates LC, 2017[77]	2017	Multicentric	6	Meeting abstract	RCT
Zabotti A, 2017[78]	2017	Italy	12	Meeting abstract	Cohort
Mease PJ, 2017[79]	2017	USA	12	Meeting abstract	Cohort

Table 1: Characteristic features of the 45 selected studies

	All articles (n=45)	Real-life studies (n=39)	RCTs (n=6)
Total number of patients	12,469	11,254	1,215
Female sex, no. (%)	6,083 (48.8)	5,588 (49.6)	495 (40.7)*
Age, mean ± SD years	51.0 ± 3.3	51.2 ± 3.3	49.2 ± 2.8*
Disease duration, mean ± SD years	8.1 ± 3.6	7.9 ± 4.0	7.9 ± 1.8*
Duration of follow-up, mean ± SD months	7.5 ± 13.5	7.8 ± 14.6	5.7 ± 0.7
Treatment assessed, no (%)			
Combined therapy bDMARDs + sDMARDs	12 (26.7)	12 (30.8)	0 (0)
bDMARDs monotherapy	17 (37.8)	11 (28.2)	6 (100)
sDMARDs monotherapy	1 (2.2)	1 (2.6)	0 (0)
Not specified treatment	15 (33.3)	15 (38.5)	0 (0)

RCT: *Randomized Clinical Trials*; SD: *Standard Deviation*; DMARDs: *Disease-Modifying Antirheumatic Drugs*; bDMARDs: *biologic DMARDs*; sDMARDs: *synthetic DMARDs.*
*Data available in only 3 studies

Frequency of MDA according to study design (observational/real life versus RCTs):

The frequency of MDA in real-life studies by the random effects model was 37%(95%-CI 34-41%), with a heterogeneity of 93%. It was observed that, in the cohort studies, despite the high heterogeneity, the frequency of patients achieving MDA status increases with observation time, varying from 25% when the outcome was evaluated at 3-4 months to 30% at 6-8. Long-term prevalence of patients reaching MDA status was 42% (95% CI 39-46%) in 12-13 months, and remained 42% (95% CI 38-45%)in studies with follow-up time over 24-months (supplementary material). In RCTs, the frequency

of MDA was 32% (95% CI 27-38%)by the random model effectwith a slightly lower but still high heterogeneity (I2 = 78%).The frequency of MDA in real-life studies and in RCTs is represented by the forest plot chart in figure 2.

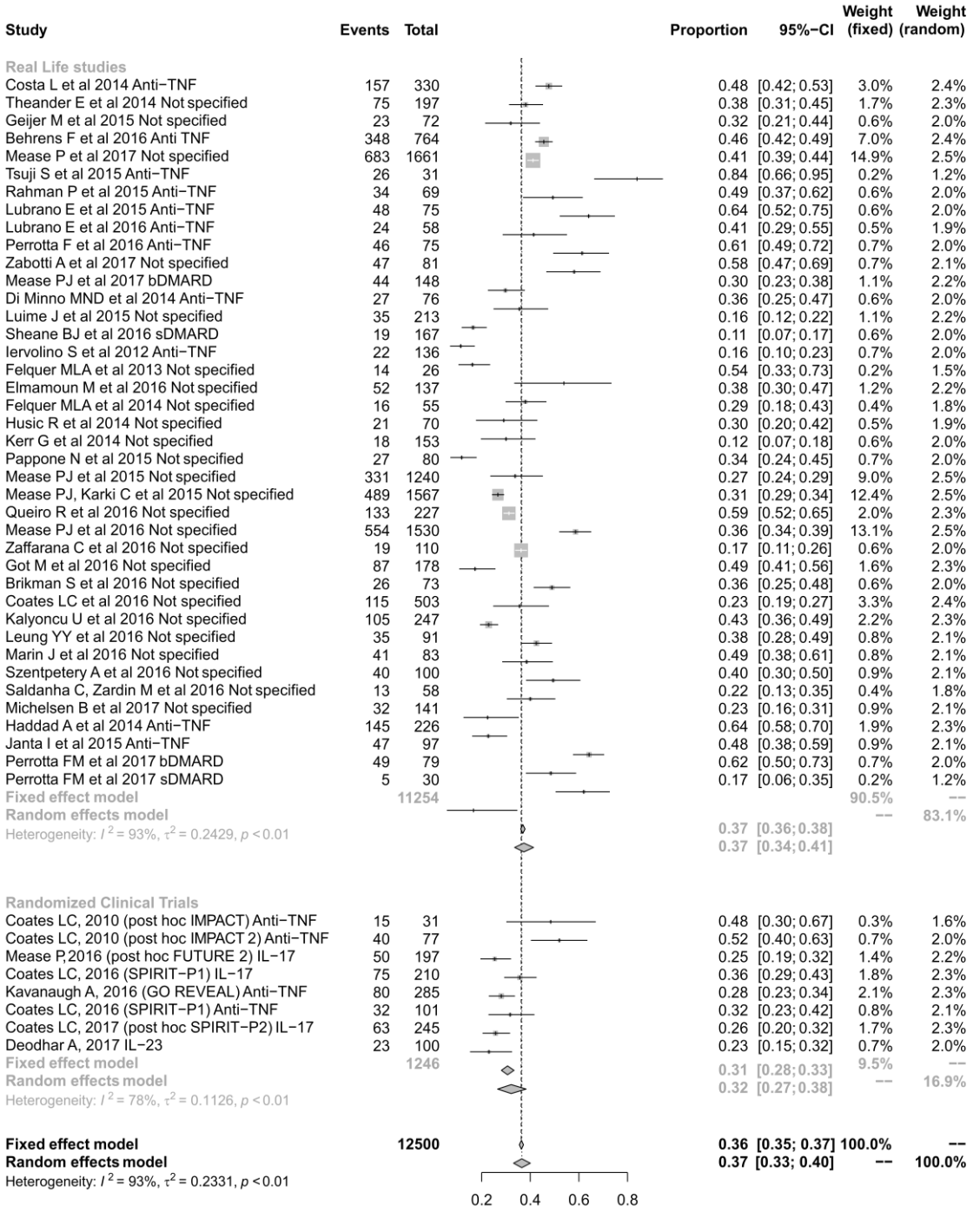

Figure 2: Frequency of patients achieving MDA status in real-life studies and in RCTs. TNF: tumor necrosis factor. bDMARD: biologic DMARD (Disease-Modified Antirheumatic Drugs). sDMARD: synthetic DMARD. IL-17: interleukin 17. IL-23: interleukin 23.

Frequency of MDA according to treatment

Analyzing by type of treatment including all follow-up times, and considering both observational and interventional trials, the frequency of MDA in patients using bDMARDs was 42% for the random effect model, I^2 = 92% (95%-CI 36-49%), and 12%, I^2 = 0% (95%-CI 8-18%), in those taking sDMARDs.

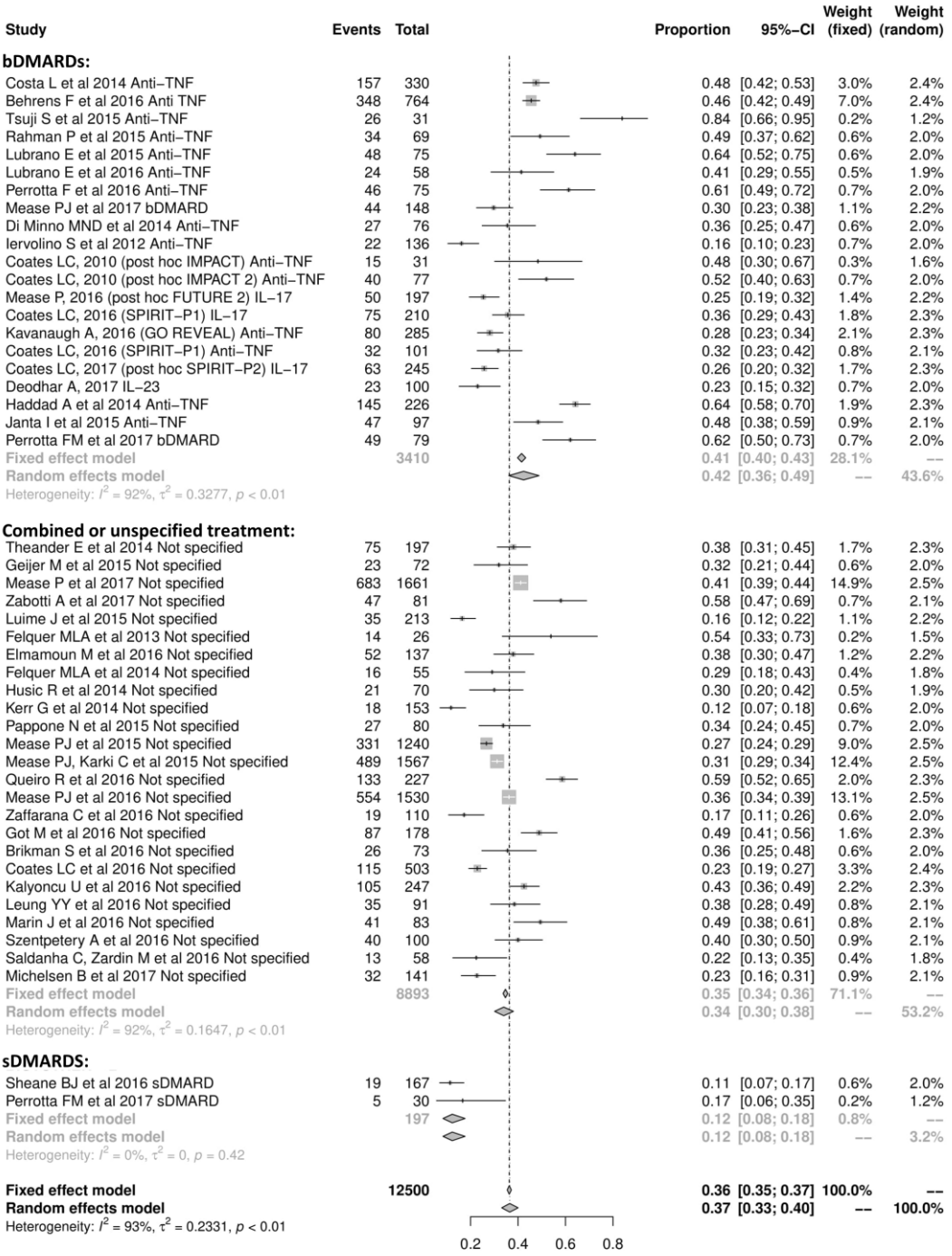

Figure 3: Frequency of MDA by type of treatment. TNF: tumor necrosis factor. bDMARD: biologic DMARD (Disease-Modified Antirheumatic Drugs). sDMARD: synthetic DMARD. IL-17: interleukin 17. IL-23: interleukin 23.

Frequency of MDA in patients taking bDMARDs in 6 months of follow-up

Considering only patients using bDMARDs, at 6 months of follow-up, using the random effects model, the frequency of MDA was 32% (95%CI 26-39%, I^2 = 79%) in RCTs, and 30% (95% CI 21-41%), I^2 = 85%) in real-life studies, according to figure 4.

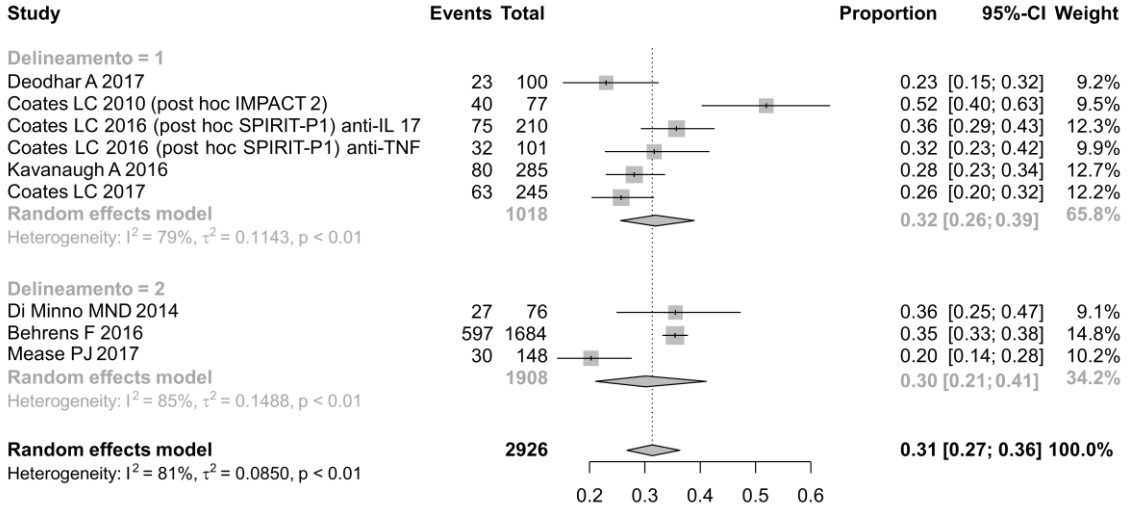

Figure 4: Frequency of MDA in patients taking bDMARDs in 6 months of follow-up. TNF: tumor necrosis factor. IL-17: interleukin 17.

Other evaluated outcomes

MDA components:

Only five studies (11.1% among the 45 articles included in the analysis) reported changes of the individual component of the MDA criteria over time (baseline, 6 and 12 months). Among them, 3 were observational and 2 were RCTs; in 4 studies, the patientswere treated with bDMARDs (with or without association with sDMARDs), and one study reported data from patients treated with methotrexate alone. Despite the small number of studies, it was possible to observe that some criteria (such as SJC, TJC, enthesitis and PASI / BSA) improved, but the patient reported outcomes (PROs), who are subjective (pain VAS, global VAS and HAQ), did not demonstrate the same response (figure 4).

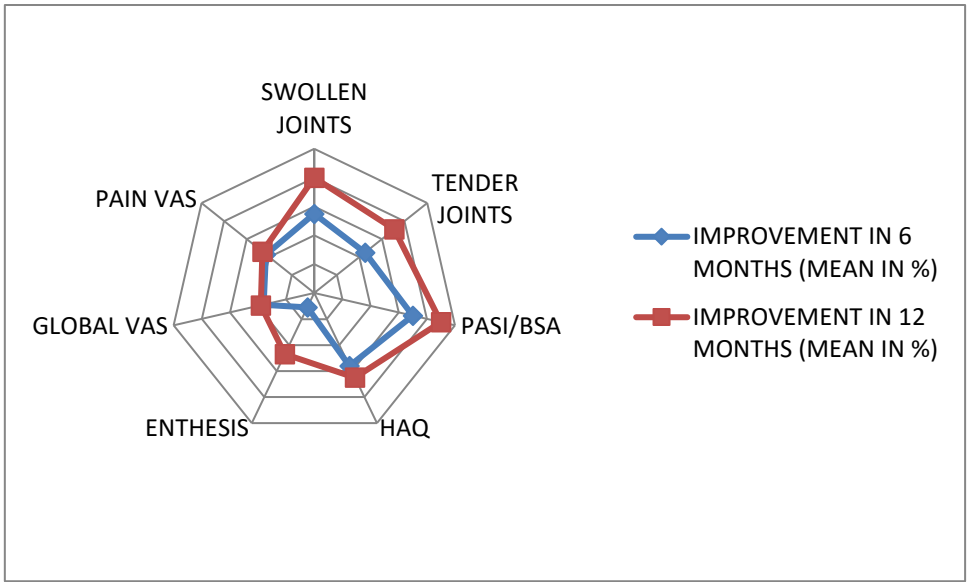

Figure 4: Average percentage of variation in each MDA domain at 6 and 12 months of evaluation.

Quality of life

Only six studies (13% among the 45 analyzed) reported SF36 MCS and SF36 PCS. Due to small number of studies, no clear association could be observed between MDA achievement and quality of life measured by SF36 (figure 5a and 5b).

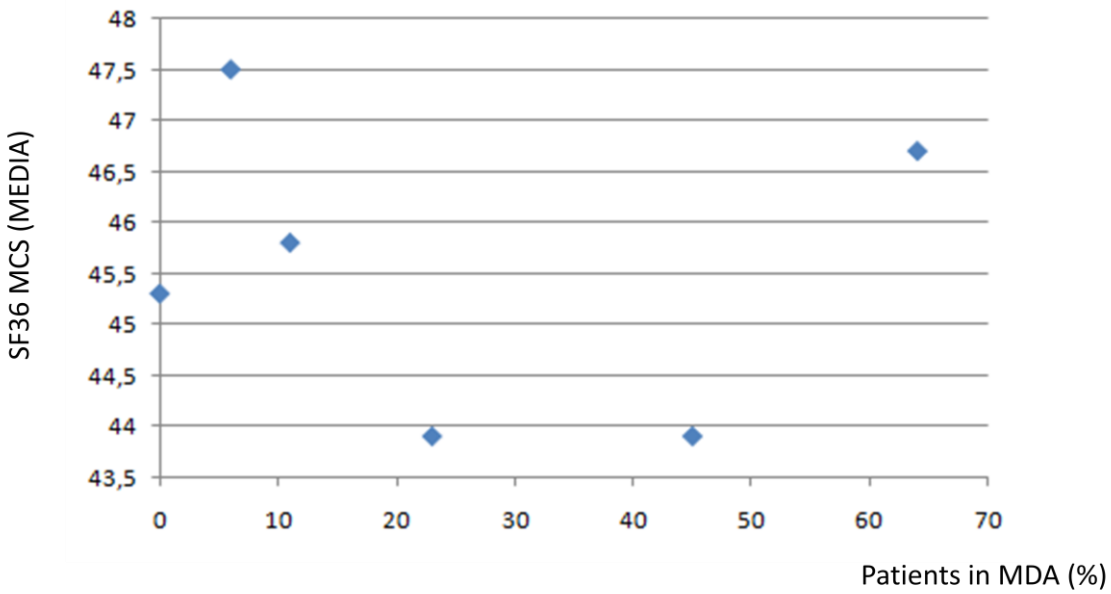

Figure 5a: scatter chart showing percentage of patients in MDA *versus* mean of SF36 MCS.

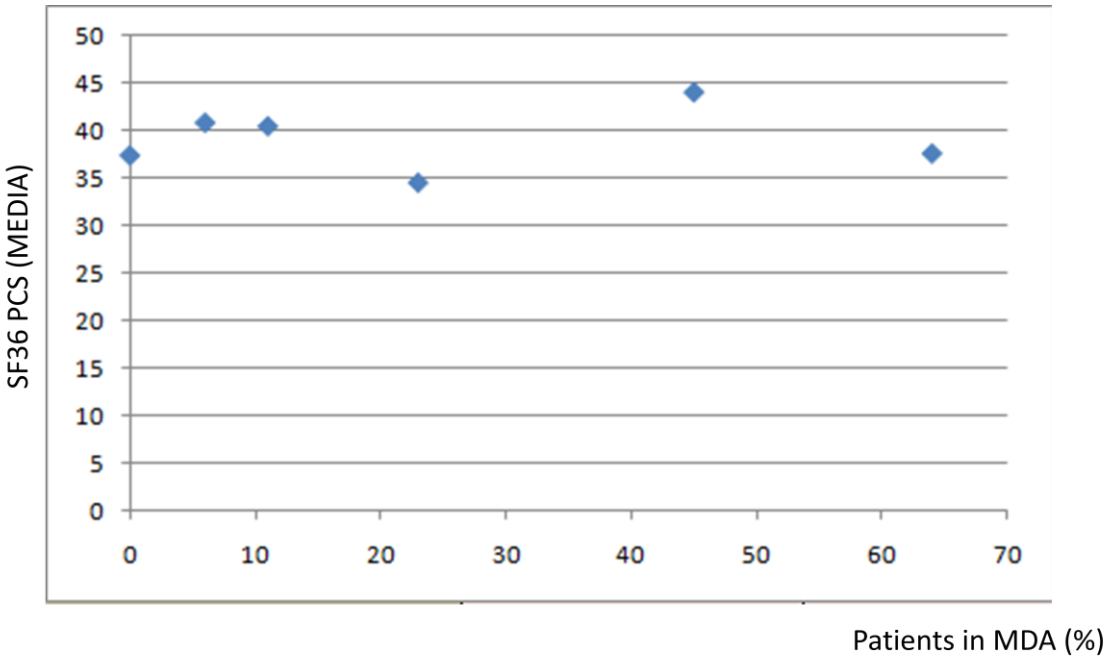

Figure 5b: scatter chart showing percentage of patients in MDA *versus* mean of SF36 PCS.

Comparison of percentage of patients in MDA *versus* DAPSA remission / low disease activity

Eleven studies (23.9%)described DAPSA values. The correlation (rS = 0,436, P = 0,119) and concordance (kappa = 0.125, P = 0.052) between percentages of remission / low activity of the two scores were calculated, and were not statistically significant, probably due to the small sample size (see table in supplementary material).

DISCUSSION

This systematic review of the literature with meta-analysis demonstrated that the frequency of patients achieving MDA status in real life/observational studies is the same that observed in RCTs, and, in cohort studies, the frequency increased over the time (25% in 3-4 months and 42% over 24-months). Due to the high heterogeneity, in this case, the meta-analysis measures could not be compared. However, we observed that, in observational / real life studies, there is a greater amplitude of effect size of individual studies, suggesting that the real-life studies are more heterogeneous.

In relation to the type of treatment, it is suggested that patients using sDMARDs have a lower frequency of MDA than those using bDMARDs, by analyzing the extent of individual effect size of each study.

It was difficult to make comparisons between studies with different designs and types of treatments due to the great heterogeneity. Observational studies, on average, have a larger population, longer follow-up time, and a greater variety of treatments compared to RCTs. Several observational studies do not even identify the type of treatment used, while most RCTs evaluate patients taking bDMARDs.

A previous publication[29] found that in RCTs the frequency of MDA varied according to the treatment used: 24-52% in patients taking anti-TNF, and 23-28% in

patients taking secukinumab (at 16 weeks). In observational studies, the frequency of MDA patients was 44-64% at 12 months, and 40% at 5-year follow-up. Another studydemonstrated that the frequency of MDA in real-life studies ranged from 15-64%[74]. These work confirm the great diversity of results found, depending on the population studied, the time of follow-up, and the type of treatment.A study performed at a Rheumatology Service of a Brazilian public hospital found that 36.2% of the patients were in MDA at least once, at 8 months of follow-up. It was also observed that there was no statistical difference in achieving MDA in patients using sDMARDs or bDMARDs[80].

With regard to the improvement of each MDA domain over time, we observed that, as previously mentioned, in general, in both real life studies and RCTs and regardless of the type of treatment, in the 6 and 12 months there was an improvement in the most indexes, such as SJC and TJC, skin and enthesitis, but the same did not occur with the PROs (global VAS, pain VAS and HAQ), which are more subjective measures.

This was the first systematic review of the literature with a meta-analysis that evaluates the frequency of MDA by type of study (real life and RCTs) and by type of treatment. To date, only a few revisions have been published about this, but no meta-analysis of the data found has been performed. Our meta-analysis has shown that the frequency of MDA patients is the same in observational / real-life studies and RCTs, and that in observational studies the frequency of MDA increases over time. In addition,it is suggested that patients using bDMARDs have a higher frequency of MDA than patients using sDMARDs (although few studies reported MDA frequency in patients using only sDMARDs), and that MDA components tend to improve, on average, over 6 and 12 months, in studies where such data were available (cohort or RCTs).

A limitation of the current work isthe great heterogeneity between the analyzed studies regarding the population included, the types of treatment and the time of follow-up. In addition, many studies did not specify the current therapy of patients included in the sample, and inmany studies the MDA was not the primary outcome to assess disease activity and only described in post hoc analysis. Furthermore, we were unable to establish a correlation between MDA and quality of life, probably because of the small number of articles that described SF36 indices. Regarding DAPSA, besides few studies describing this disease activity score, we were unable to establish a positive association between DAPSA remission / low activity and MDA.

CONCLUSION

In conclusion, this systematic literature review demonstrated that, indeed, the frequency of MDA in real-life studies is the same than in RCTs, and it is suggested to be higher in patients using bDMARDs than in sDMARDs. This finding suggests that MDA is a useful treatment target for PsA in the real-life context.

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Supplementary material:

1. Risk assessment of bias

1.1. Randomized Clinical Trials: Cochrane Collaboration tool for risk assessment of bias in randomized clinical trials

Study	Cochrane Collaboration tool for risk assessment of bias in randomized clinical trials						
	SELECTION BIAS		PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	OTHER BIAS
	Random sequence generation	Allocation concealment	Participants and professionals blinding	Outcome assessors blinding	Incomplete outcome data	Selective reporting	Other bias
Coates LC, 2010	Unclear	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Unclear
A. Deodhar	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear
Coates LC, 2016	Unclear	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Unclear
Coates LC, 2017	Unclear	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Unclear
Kavanaugh, A	Unclear	Unclear	High Risk	High Risk	High Risk	Low Risk	Unclear
Mease PJ 2016	Unclear	Unclear	Unclear	Unclear	Unclear	Low Risk	Unclear

1.2. Cohort studies: NewCastle-Ottawa Scale

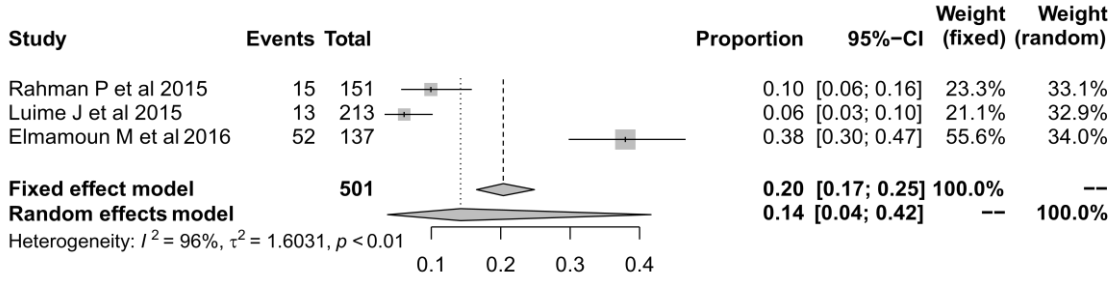
Study	NEWCASTLE-OTTAWA SCALE							
	SELECTION				COMPARABILITY	OUTCOME		
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Elmamoun,M	b	c	b	b	b	c	b	d
Theander, E	b	a	d	a	b	b	a	d
Mease, PJ	a	a	a	a	b	b	a	d
Behrens F	b	a	a	a	b	b	a	d
Geijer M	a	c	a	b	b	b	a	b
Iervolino S	a	a	b	b	b	b	a	b
Perrota F	a	c	a	a	b	b	a	b
Sheane BJ	a	c	a	a	b	b	a	b
Zabotti A	b	a	a	b	b	b	a	d
Costa L	a	a	b	a	b	b	a	a
Di Minno MND	a	a	b	a	b	b	a	a
Felquer MLA	a	a	b	a	b	b	a	a
Lubrano E, 2015	a	a	b	a	b	b	a	c
Lubrano E, 2016	b	a	b	a	b	b	a	b
Luime J	d	a	a	b	b	d	a	d
Mease PJ, 2017	a	a	a	a	b	b	a	a
Rahman P	b	a	a	b	b	d	a	a
Tsuji S	a	a	d	b	b	d	a	a

1.3 Cross-Sectional studies: NewCastle-Ottawa Adapted Scale

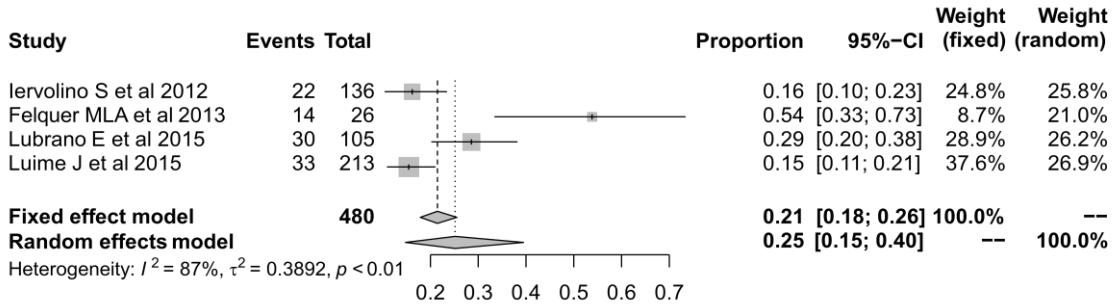
	NEWCASTLE OTTAWA ADAPTED SCALE						
	SELECTION				COMPARABILITY	OUTCOME	
Study	Sample representativeness	Sample size	Non-responders	Ascertainment of the exposure (risk factor)		Assessment of the outcome	Statistical test
Felquer MLA	a	a	a	a	b	b	a
Queiro R	b	b	c	a	b	b	a
Mease PJ, 2016	b	b	a	a	b	b	a
Brikman, S	b	b	a	a	a	b	a
Coates, LC	a	b	a	a	b	b	a
Janta I	b	b	a	a	b	a	a
Leung YY	b	b	a	a	b	b	a
Marin J	b	b	a	a	a	b	a
Michelsen B	a	b	a	a	b	a	a
Saldanha C	b	b	a	a	b	b	a
Perrotta FM	b	b	a	a	b	b	b
Mease PJ, 2015	b	b	a	a	b	b	a
Szentpetery A	b	b	a	a	b	b	a
Mease PJ, 2015	a	a	a	a	b	d	a
Got M, 2016	a	a	c	a	b	d	a
Haddad A	a	a	a	a	b	b	a
Husic R	a	a	c	a	b	b	a
Kalyoncu U	a	a	a	a	b	b	a
Kerr G	a	a	a	a	b	b	a
Pappone N	a	a	a	a	b	b	a
Zaffarana C	a	a	c	a	b	b	a

2. Frequency of MDA in cohort studies by time of treatment:

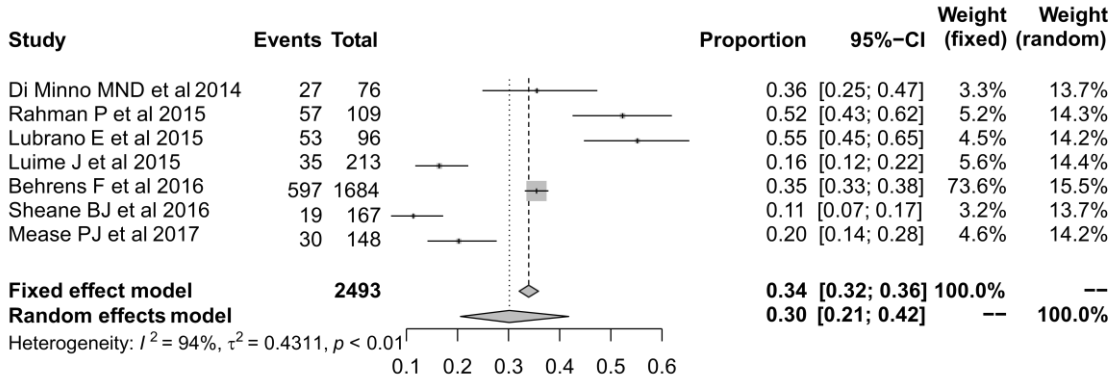
2.1 Baseline



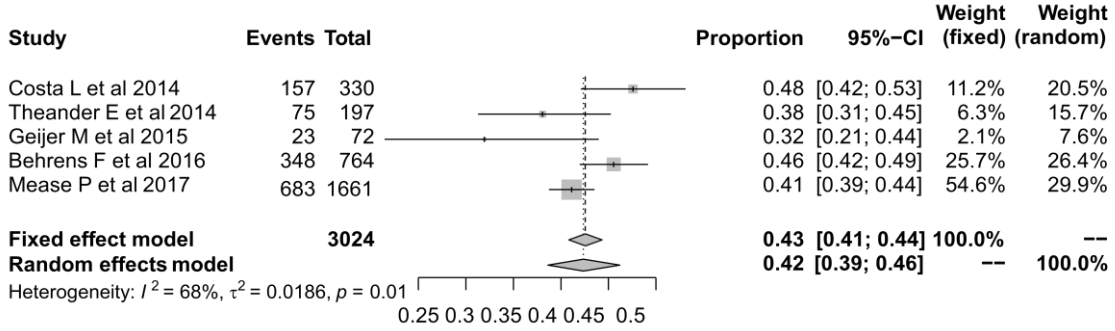
2.2 3-4 months



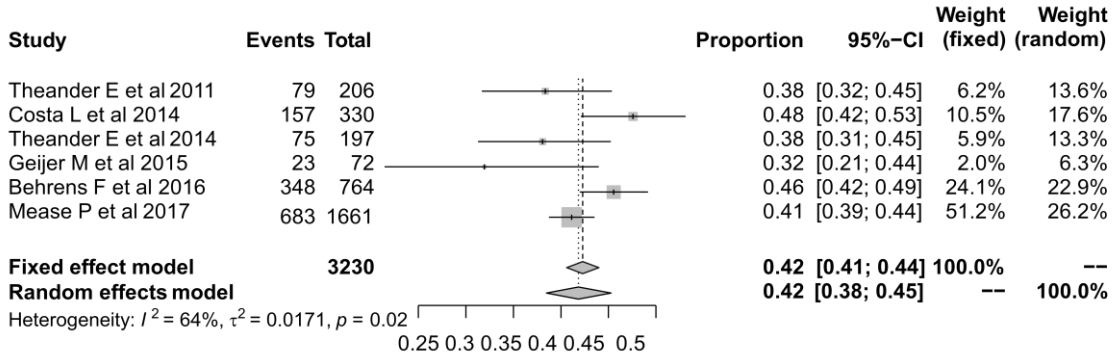
2.3 6-8 months



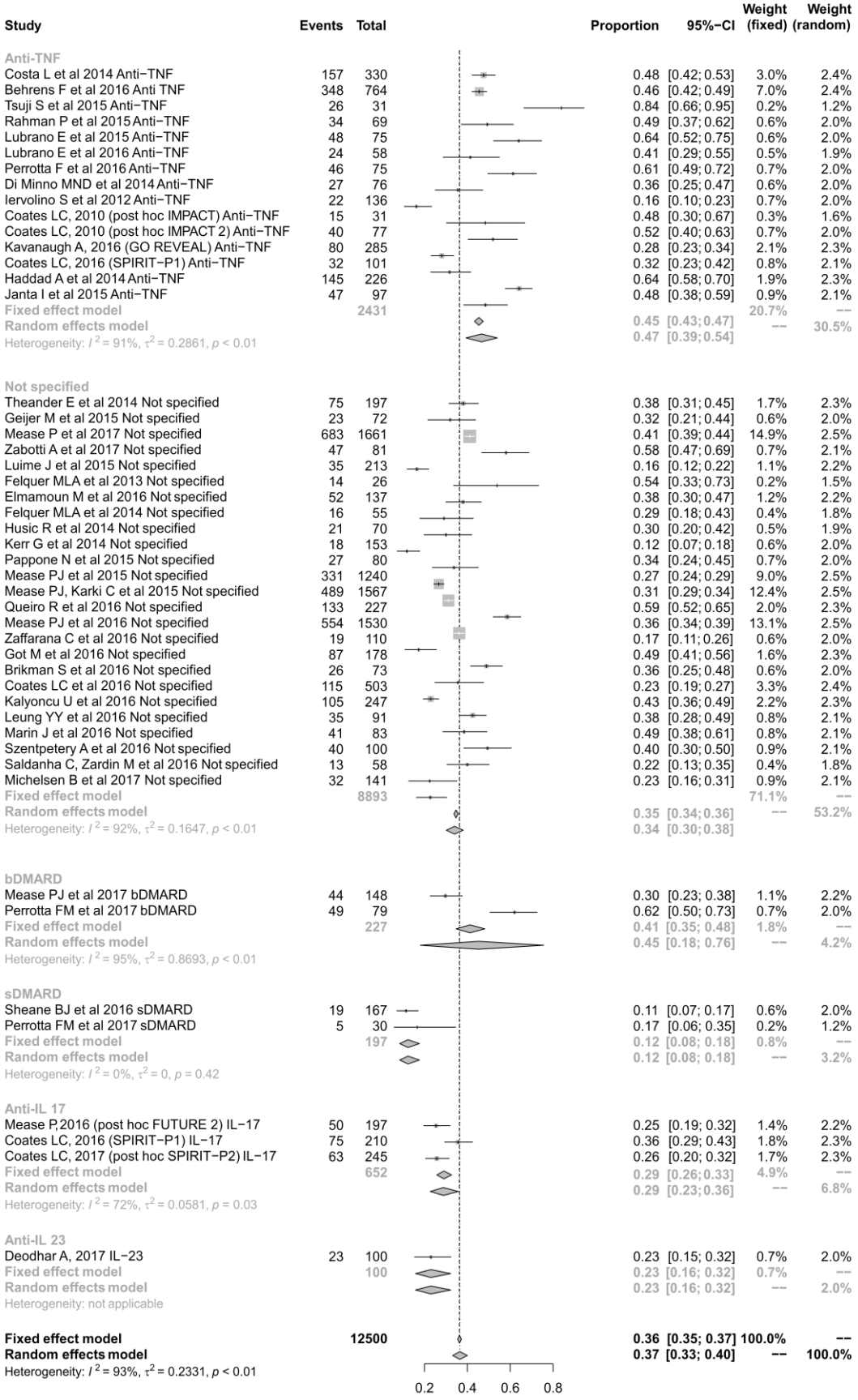
2.4 12-13 months



2.5 24-60 months



3. Frequency of MDA by type of treatment



4. Table 2x2 MDA versus DAPSA remission / low activity or moderate / high activity

AUTHOR	YEAR	FOLLOW-UP TIME (MONTHS)	MDA		DAPSA	
			YES	NO	REMISSION / LOW ACTIVITY	MODERATE / HIGH ACTIVITY
Theander E et al	2011	0	0	206	88	118
		60	79	127	88	118
Brikman S et al	2016	0	26	47	60	13
Geijer M et al	2015	0	0	72	0	72
		50	23	49	29	43
Janta I et al	2015	0	47	55	102	0
Leung YY et al	2016	0	35	63	98	0
Lubrano E et al	2015	0	0	124	0	124
Lubrano E et al	2016	0	0	58	0	58
Michelsen B et al	2017	0	32	109	141	0
Perrotta F et al	2016	0	46	29	0	75
Theander E et al	2014	0	22	175	0	197
		60	75	122	197	0
Perrotta FM et al	2017	0	54	55	79	30

8. CONSIDERAÇÕES FINAIS

O presente estudo demonstrou que a freqüênciade MDA é semelhante em estudos de vida real e em ECRs. Além disso, demonstrou que, quanto maior o tempo de acompanhamento, maior tende a ser a freqüência de MDA. O tratamento com bDMARDstambém mostrou ser numericamente superior ao tratamento com sDMARDs. Nosso estudo apresentou uma grande heterogeneidade entre os estudos selecionados, o que pode ter influenciado alguns resultados.

Não foi possível estabelecer se um maior número de pacientes em MDA se reflete em melhores índices de qualidade de vida. Poucos estudos apresentavam dados sobre qualidade de vida, e, esses poucos, não fizeram essa associação entre MDA e qualidade de vida, apenas descreveram os dados em tabelas ao longo do tempo.

Em relação aos componentes do MDA, notou-se que a maioria dos índices apresentou melhora ao longo do tempo, porém isso não aconteceu nos índices mais subjetivos, como VAS global, VAS de dor e HAQ. A avaliação subjetiva por parte dos pacientes, muitas vezes, pode estar relacionada com deformidades ou incapacidades permanentes já adquiridas com a progressão clínica da doença, ou mesmo com dores ou manifestações de outras comorbidades. Isso pode refletir na freqüência de pacientes em MDA, podendo inclusive subestimar esse número.

9. PERSPECTIVAS FUTURAS

De um modo geral, o MDA apresenta-se como bom alvo terapêutico na AP, e deve ser utilizado também na nossa prática clínica, pois é de fácil execução, compreende a maioria dos domínios da AP, e é factível de ser realizado em vida real.

O MDA deve ser usado como alvo de tratamento, pois já foi demonstrado em estudos prévios que o MDA está associado a melhores desfechos articulares, cutâneos, e também com melhora em alguns índices de qualidade de vida e função, embora aparente ter uma associação com maior uso de medicamentos biológicos, e, assim, com maior incidência de eventos adversos.

Mais estudos deverão ser realizados, principalmente em vida real, e também buscando avaliar se há correlação entre MDA e melhora nos índices de qualidade de vida.

10. ANEXOS E/OU APÊNDICES

10.1 Anexo 1: Escalas de avaliação metodológica

10.1.1Escala Newcastle Ottawa para estudos de Coorte

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community □

b) somewhat representative of the average _____ in the community □

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort □

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) □

b) structured interview □

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes□

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) □

b) study controls for any additional factor □ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment □

b) record linkage □

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) □

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for □

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) □

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

10.1.2 Escala Newcastle Ottawa adaptada para estudos Transversais

1) Representativenessofthesample:
   a) Truly representative of the average in the target population. * (all subjects or randomsampling)
   b) Somewhat representative of the average in the target population. * (non- randomsampling)
   c) Selectedgroupofusers.
   d) No description of the samplingstrategy.
2) Samplesize:
   a) Justifiedand satisfactory.*
   b) Notjustified.
3) Non-respondents:
   a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory.*
   b) The response rate is unsatisfactory, or the comparability between

respondents and non-respondents isunsatisfactory.

c) No description of the response rate or the characteristics of the responders and thenon-responders.

4) Ascertainment of the exposure (riskfactor):

a) Validatedmeasurement tool.**

b) Non-validated measurement tool, but the tool is available ordescribed.*

c) No description of the measurementtool.

Comparability:(Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors arecontrolled.

a) The study controls for the most important factor (select one).*

b) The study control for any additional factor.*

Outcome:(Maximum 3 stars)

1) Assessmentoftheoutcome:

a) Independentblindassessment.**

b) Recordlinkage.**

c) Self report.*

d) Nodescription.

2) Statisticaltest:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value).*

b)The statistical test is not appropriate, not described orincomplete.

10.2 Check-list PRISMA

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5-6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	13
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	20
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	31
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.	32
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.	32
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	32
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).	32
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.	33
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	33
Risk of bias in 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.	33

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	33-34
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	33-34
Section/topic	#	Checklist item	Reported on page #
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).	33
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	33-34
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.	34
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.	35-37
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	50
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	37-40
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	37-40
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	50
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	40-42
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).	42-43
Limitations	25	Discuss limitations at study and outcomelevel (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	42-43
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	43
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.	-