Title: Prevalence of psoriatic arthritis patients achieving minimal disease activity in real-life studies and randomized clinical trials: systematic review with metanalysis

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Running head: MDA: real-life vs. RCT

Key words: psoriatic arthritis, randomized controlled trials, observational studies, systematic reviews

Institution: Hospital de Clínicas de Porto Alegre (HCPA), Rheumatology Department

Support: Fundo de Incentivo à Pesquisa e Eventos do HCPA

Conflict of interest: Authors declare no conflicts of interest.

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Prevalence of psoriatic arthritis patients achieving minimal disease activity in real-life studies and randomized clinical trials: systematic review with meta-analysis

ABSTRACT

Objective: To estimate the frequency of patients achieving MDA status in real-life studies and RCTs.

Methods: a systematic literature search from 2009-2017 was performed in Pubmed, Embase, Cochrane Library and Lilacs. Study selection and data extraction were performed by two independent researchers. Random effects single-arm meta-analyses were performed and heterogeneity was assessed using I^2.

Results: 405 records were identified, 45 studies were analyzed: 39 (86.7%) observational studies and 6 RCTs (13.3%); they included 12,469 patients. The overall prevalence of MDA in cross-sectional studies was 35% (95%CI 30-41%, I^2=94%), varying from 17% (95%CI 7-34%) in patients taking sDMARDs to 57% (95%CI 41-71%) in those on bDMARDs. Prevalence of MDA in cohort studies increased with longer follow-up time, ranging from 25% (95%CI 15-40%) with a 3-4 months follow up to 42% (95%CI 38-45) with > 24 months follow-up. PsA patients receiving bDMARDs in real-life context and RCTs had similar prevalence of MDA at 6 months follow-up: 30% (95%CI 21-41%, I^2=85%) versus 32% (95% CI 26-39%, I^2=79%), respectively.

Conclusion: PsA patients included in real-life studies published in the last years have similar prevalence of MDA than those participating in controlled clinical trials. This finding suggests that MDA is a useful treatment target for PsA in the real-life context.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease that affects about 20-33% of individuals with psoriasis, and approximately 133 in every 100,000 individuals of the world population[1,2]. PsA has heterogeneous manifestations, affecting peripheral and axial joints, skin, nails, and entheses[3].

The minimal disease activity (MDA) criteria have been recommended as therapeutic target in PsA[4,5]. 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 or body surface area (BSA) ≤3; patient pain visual analog scale (pain VAS) score≤15; patient global disease activity (global VAS) score ≤20; health assessment questionnaire (HAQ) score ≤0.5; and tender entheseal points ≤1[6].

The prevalence of MDA has been assessed in several trials and its frequency varies according to the study design, drug and time of evaluation. According to a recent publication, the frequency of MDA in randomized controlled trials (RCT) varies from 24% to 52% with tumor necrosis factor (TNF) inhibitor therapy and from 14% to 41% with secukinumab; and from 40 to 64% in observational studies[7].

Participants of RCTs usually present higher levels of disease activity, fewer comorbidities[8], and better adherence rates to therapy than patients analyzed in observational studies[9]. In real life, several factors such as poor adherence and restricted access to drugs preclude the achievement of the MDA status in a treat-to-target (T2T) strategy[10]. The aim of the current investigation is to analyze the frequency of PsA patients achieving MDA status in real-life studies and RCTs.

MATERIALS AND 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 international prospective register of systematic reviews (PROSPERO) record number 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 from 2009 to 2017 in 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) was carried out.

Inclusion criteria: original studies reporting the prevalence of MDA status among adult patients with PsA.

Exclusion criteria: i) duplicates (in case of duplicates, the most complete publication was included, e.g., in case of abstracts and original articles reporting the same results, only the complete original article results were considered); ii) review articles, letter to editor, case reports; iii) articles not describing MDA according to Coates[6], 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 (MZ and CK) independently selected the articles by title and abstract. In the next step, two researchers (MZ 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, time of evaluation, number and percentage of participants achieving the MDA status, mean and standard deviation (SD) of each component of MDA criteria. The type of treatment was assessed and classified as biologic disease modifying rheumatic drug (bDMARDs) monotherapy, synthetic DMARD (sDMARDs) monotherapy, combined bDMARDs + sDMARDs therapy, non-steroidal anti-inflammatory drugs (NSAIDs) and unspecified treatment.

These data were independently extracted from articles by two reviewers (MZ and CS), and the discordances were solved by consensus.

Statistical analyses:

Observational trials: To analyze the prevalence of MDA in observational trials, a single-arm meta-analysis was performed, grouping both cohort and cross-sectional

studies and including all observational trials irrespective of treatment evaluated. The final follow-up time of each cohort study was considered in the analysis.

Subsequently, the studies were separated according to design: a single-arm meta-analysis including only cross sectional studies was performed and another analysis including only cohort studies according to follow-up time (baseline, 3-4 months, 6-8 months, 12-13 months, and 24-60 months) was conducted.

Randomized clinical trials (RCTs): Single-arm meta-analysis was performed to estimate the frequency of MDA in RCTs, considering maximum follow-up time and including all RCTs irrespective of treatment evaluated.

A single-arm meta-analysis was also performed to analyze the frequency of MDA in patients treated with bDMARDs in real-life studies and RCTs at 6 months follow-up.

The results of the meta-analyses were represented by forest plots. I^2 index was used to assess heterogeneity. When relevant heterogeneity was found (I^2 index $\geq$ 50%), the results from the random effects model were showed, and, in cases where I^2 was <50%, the fixed effects model was used[11].

RESULTS

A total of 405 records 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. The forty-five eligible titles included in the final analysis are listed in the table 1.

The flow chart summarizing the selection of studies is shown in Figure 1.

The 45 selected studies included 12,469 patients, mean age (SD) 51.0 (±3.3) years old, mostly men (N= 6,386, 51.2%) with a mean PsA duration (SD) of 8.1 (±3.6) years. Thirty-nine (86.7%) were real-life studies and only 6 (13.3%) were RCTs. Observational studies, on average, had larger population and longer follow-up time compared to RCTs. Among the 39 observational studies, 19 (48.7%) and 10 (25.6%) were carried out in the Europe and North America, respectively, and 37 (94.9%) were conducted in university hospitals.

The characteristics of the studies included in the analysis are shown in table 2.

The assessment of bias is described in supplementary table 1-3.

Frequency of MDA in real-life studies.The frequency of PsA patients achieving MDA status in real-life studies was 37% (95%-CI 34-41%, I^2=93%) when both cross-sectional and cohort studies were grouped and all types of treatment were considered. When only cross-sectional studies were considered (N=22), the overall frequency of MDA was 35% (95%-CI 30-41%, I^2=94%) (Figure 2), varying from 17% (95%CI 7-34%) in the sole study which specified that patients were taking sDMARDs to 57% (95%CI 41-71%, I^2=87%) in studies evaluating patients in use of anti-TNF therapy. The assessment of the prevalence of MDA in the real-life context in different subgroups of treatment was restricted because 81.8% (N=18) of cross-sectional studies did not specify the current therapy of patients.

In cohort studies, the frequency of patients in MDA increased with longer follow-up time, varying from 25% (95%CI 15-40%, I^2=87%) when MDA was evaluated at 3-4 months, 30% (95%CI 21-42%, I^2=94%) at 6-8 months, 42% (95% CI 39-46%, I^2=68%) in 12-13 months, and 42% (95% CI 38-45%, I^2=64%) in studies with ≥ 24-months follow-up (Supplementary Figure 1). When patients treated with biological

drugs in cohort studies were compared to those treated with bDMARDs in RCTs the frequency of MDA was similar at 6 months follow-up: 30% (95%CI 21-41%, I^2=85%) versus 32% (95% CI 26-39%, I^2=79%), respectively (Supplementary Figure 3).

Frequency of MDA in randomized clinical trials (RCTs). The 6 titles included in the analysis evaluated 7 RCTs (one manuscript reported the results of two RCTs) and all were trials evaluating biologic therapy. When all biological therapies (anti-TNF, anti-IL17 and anti-IL12/23) were grouped, the prevalence of PsA patients in MDA status was 32% (95%-CI 27-38%, I^2=78%) in the biological therapy arm, in contrast with only 9% of patients in MDA in the placebo group (95%-CI 5-15%, I^2 78%), in approximately 6 months follow-up period (Figure3). The prevalence of MDA was similar across bDMARDs: 30% (95%-CI 27-51%, I^2=83%) in studies evaluating anti-TNF therapy, 29% (95%-CI 23-36%, I^2=72%) in those evaluating anti-IL17 drugs and 23% (95%-CI 16-32%, I^2 not applicable) in the sole study evaluating anti-IL12-23 therapy included in the analysis (Supplementary Figure 2).

DISCUSSION

To our best knowledge, this is the first systematic literature review with meta-analysis to compare MDA performance in RCTs and observational studies. Knowing how MDA performs in RCTs and real-life scenarios may contribute to improve its feasibility. The present work demonstrated that approximately one third of PsA patients evaluated in cross-sectional studies were in MDA, with this value varying from 17% (95%CI 7-34%) with the use of sDMARDs to 57% (95% CI 41-71%) with bDMARDs. In addition, the longer the follow-up time in real-life studies, the higher the prevalence of patients reaching MDA. Patients on bDMARDs had similar prevalence of MDA status at 6 months follow-up in RCTs and observational studies.

The initial hypothesis previewed a higher frequency of MDA in RCTs, due to better adherence to therapy since presence of barriers to medication acquisition and cost of therapy can be a problem in daily life. However, even in RCTs, adherence rates can range from 43-78% among patients receiving treatment for chronic diseases. Factors that are related to lower adherence in RCTs and real-life studies include psychiatric comorbidities, cognitive impairment, inadequate follow-up, adverse effects of medication, poor physician-patient relationship, missed appointments, and treatment complexity[9].

Patients included in RCTs usually have higher levels of disease activity than in real-life studies[55], and this may negatively impact the final outcome of the studies[8], preventing patients from reaching MDA status.

On the other hand, in real life studies we expect lower response because of lower adherence, but in this case, mostly patients have milder disease. So, we expect lower response because of lower adhesion but higher response as disease is milder and treatment is open label.

In the present work, RCTs and real-life studies had similar frequency of MDA probably because the selected observational studies were mostly carried out in university hospitals located in developed countries, where PsA patients have adequate educational level, receive high quality standard of care and have easy access to DMARDs. In underdeveloped countries, in contrast, restricted access to DMARDs and low educational level leading to poor understanding of medication instructions were barriers to achieve MDA status in the real-life context[10].

Our results were similar to that previously reported in a study[12] which described the frequency of MDA in RCTs varying from 24 to 52% in patients taking anti-TNF, and from 23 to 28% in those receiving secukinumab (at 16 weeks). In observational

studies, the frequency of MDA was 44-64% at 12 months, and 40% at 5-year follow-up[7]. Another study demonstrated that the frequency of MDA in real-life studies ranged from 15-64%[49].

Limitations to the current work are the great heterogeneity found in included studies regarding characteristics of patients, current therapy and follow-up time. There was larger amplitude in effect size among observational studies compared to RCTs, suggesting that the group composed by real-life studies was more heterogeneous. In addition, the vast majority of real-life studies did not specify the current treatment of patients neither reported MDA in different subgroups of treatment. Furthermore, in many studies, the assessment of MDA was not the primary outcome and its prevalence was only described in post hoc analysis.

A priori, observational studies are expected to have greater heterogeneity due to the role of several uncontrolled factors influencing MDA achievement. The lack of a standardized treatment protocol within the same study and across various scenarios is itself a key factor to explain different results. Also, in cohort and case-control studies, missing data may be large enough to impact the outcome and no imputation is usually reported.

Moreover, we acknowledge that in this case clinical heterogeneity should be considered as a limitation to the lack of statistical homogeneity. Variances in inclusion criteria could impact MDA achievement even with similar treatment strategy protocols. This is particularly relevant in RCTs. For example, in the IMPACT trial, 5 or more swollen/tender joints were considered as inclusion criteria, whereas, in FUTURE-2 and SPIRIT-P1, 3 or more tender/swollen joints were necessary to participate in the studies. Besides, previous treatment differed among studies. For instance, in FUTURE-2, participants could have failed nonsteroidal anti-inflammatory drugs, synthetic DMARDs or TNF inhibitors, in SPIRIT-P1, they had to be TNF-inhibitor-naïve, and, in SPIRIT-P2, they were only included after a TNF inhibitor inadequate response.

In conclusion, PsA patients included in real-life studies published in the last years have similar prevalence of MDA than those participating in controlled clinical trials. This finding suggests that MDA is a useful treatment target for PsA in the real-life context.

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Table 1: The 45 studies included in the analysis

AUTHOR	YEAR	COUNTRY	FOLLOW-UP TIME (MONTHS)	PUBLICATION TYPE	STUDY DESIGN
Felquer MLA, 2014[3]	2014	Argentina	0	Original article	Cross-sectional
Mease P, 2017[12]	2017	USA	36	Meeting abstract	Cohort
Tsuji S, 2015[13]	2015	Japan	13	Meeting abstract	Cohort
Queiro R, 2016[14]	2016	Spain	0	Meeting abstract	Cross-sectional
Elmamoun M, 2016[15]	2016	Ireland	0	Meeting abstract	Cohort
Deodhar A, 2017[16]	2017	USA/ Switzerland	6	Meeting abstract	RCT
Di Minno MND, 2014[17]	2014	Italy	6	Original article	Cohort
Rahman P, 2015[18]	2015	Canada	12	Meeting abstract	Cohort
Mease PJ, 2016[19]	2016	USA	0	Meeting abstract	Cross-sectional
Behrens F, 2016[20]	2016	Germany	24	Meeting abstract	Cohort
Zaffarana C, 2016[21]	2016	Argentina	0	Meeting abstract	Cross-sectional
Felquer MLA, 2013[22]	2013	Argentina	3	Meeting abstract	Cohort
Got M, 2016[23]	2016	Canada	0	Meeting abstract	Cross-sectional
Brikman S, 2016[24]	2016	Israel	0	Original article	Cross-sectional
Coates LC, 2010 (post hoc IMPACT 2)[6]	2010	United Kingdom	6	Original article	RCT
Coates LC, 2016[25]	2016	United Kingdom	0	Original article	Cross-sectional
Coates LC, 2016 (post hoc SPIRIT-P1)[26]	2016	United Kingdom	6	Meeting abstract	RCT
Costa L, 2014[27]	2014	Italy	24	Original article	Cohort

Geijer M, 2015[28]	2015	Sweden	60	Original article	Cohort
Haddad A, 2014[29]	2014	Canada	0	Original article	Cross-sectional
Husic R, 2014[30]	2014	Austria	0	Original article	Cross-sectional
Iervolino S, 2012[31]	2012	Italy	3	Original article	Cohort
Janta I, 2015[32]	2015	Spain	0	Original article	Cross-sectional
Kalyoncu U, 2016[33]	2016	Turkey	0	Original article	Cross-sectional
Kavanaugh A, 2016[34]	2016	Multicentric	6	Original article	RCT
Kerr G, 2014[35]	2014	USA	0	Original article	Cross-sectional
Leung YY, 2016[36]	2016	Singapore	0	Original article	Cross-sectional
Lubrano E, 2015[37]	2015	Italy	12	Original article	Cohort
Lubrano E, 2016[38]	2016	Italy	12	Original article	Cohort
Marin J, 2016[39]	2016	Argentina	0	Original article	Cross-sectional
Michelsen B, 2017[40]	2017	USA/Norway	0	Original article	Cross-sectional
Pappone N, 2015[41]	2015	Italy/Israel	0	Original article	Cross-sectional
Perrotta F, 2016[42]	2016	Italy	12	Original article	Cohort
Sheane BJ, 2016[43]	2016	Canada	6	Original article	Cohort
Theander E, 2014[44]	2014	Sweden	60	Original article	Cohort
Mease PJ, 2015[45]	2015	USA	0	Meeting abstract	Cross-sectional
Mease PJ, Karki C, 2015[46]	2015	USA	0	Meeting abstract	Cross-sectional
Luime J, 2015[47]	2015	Netherlands	6	Meeting abstract	Cohort
Szentpetery A, 2016[48]	2016	Ireland	0	Meeting abstract	Cross-sectional
Saldanha C, Zardin	2016	Brazil	0	Meeting abstract	Cross-

M, 2016[49]					sectional
Mease PJ, 2016[50]	2016	Multicentric	4	Meeting abstract	RCT
Perrota FM, 2017[51]	2017	Italy	0	Meeting abstract	Cross-sectional
Coates LC, 2017[52]	2017	Multicentric	6	Meeting abstract	RCT
Zabotti A, 2017[53]	2017	Italy	12	Meeting abstract	Cohort
Mease PJ, 2017[54]	2017	USA	12	Meeting abstract	Cohort

Table 2: Characteristics features of the 45 selected titles according to study design

	All articles (n=45)	Real-life studies (n=39)	RCT (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 bDMARD + sDMARD	12 (26.7)	12 (30.8)	0 (0.0)
bDMARD monotherapy	17 (37.8)	11 (28.2)	6 (100)
sDMARD monotherapy	1 (2.2)	1 (2.6)	0 (0.0)
Treatment not specified	15 (33.3)	15 (38.5)	0 (0.0)

RCT: randomized clinical trials; SD: standard deviation; bDMARD: biologic disease-modifying antirheumatic drug; sDMARD: synthetic disease-modifying antirheumatic drug. *Data available in only 3 studies.

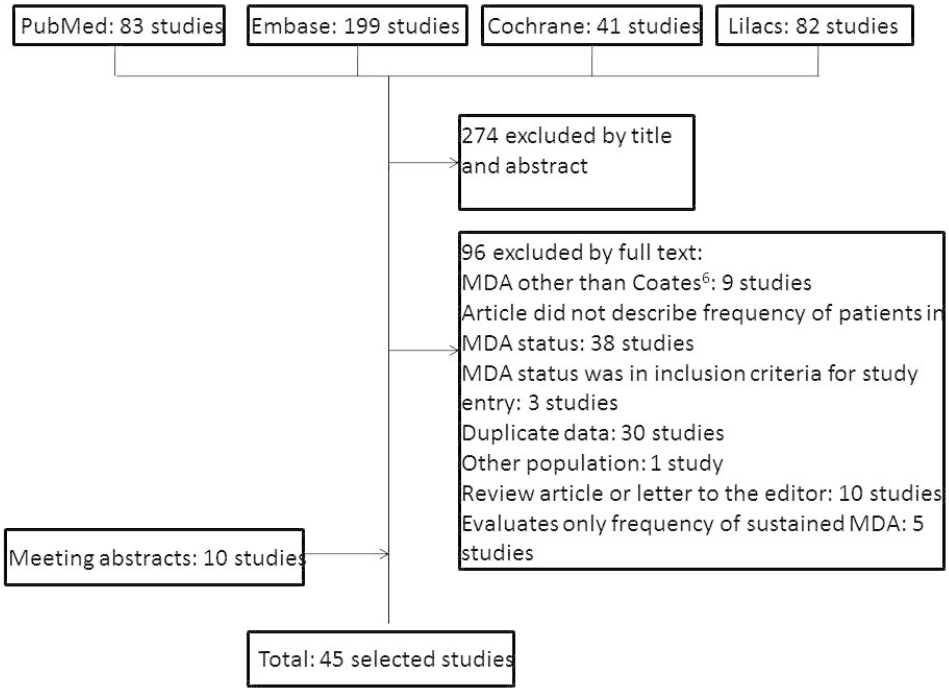

Figure 1: Flow chart showing the selection of studies for inclusion in the meta-analysis

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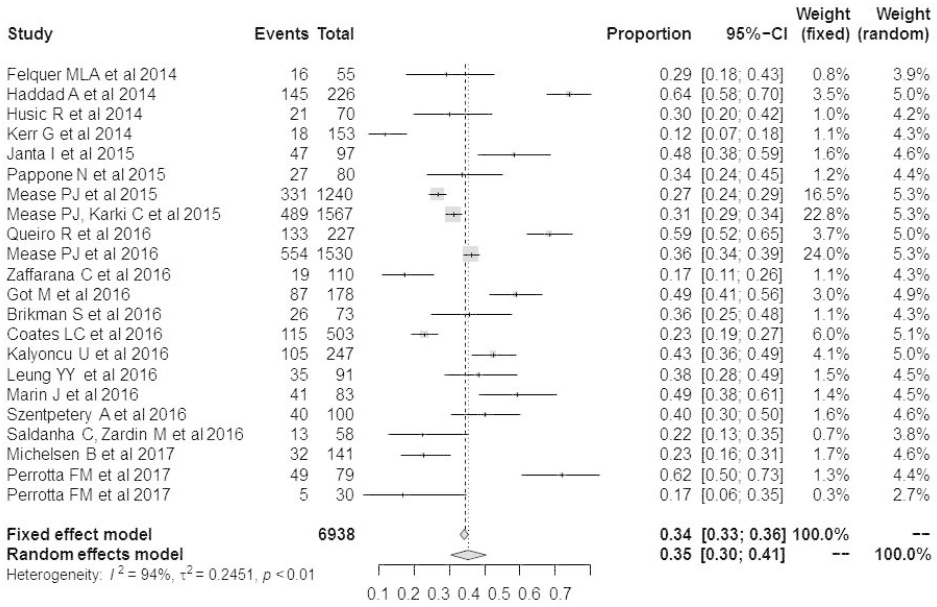

Figure 2: Prevalence of patients in minimal disease activity in real life studies with cross-sectional design

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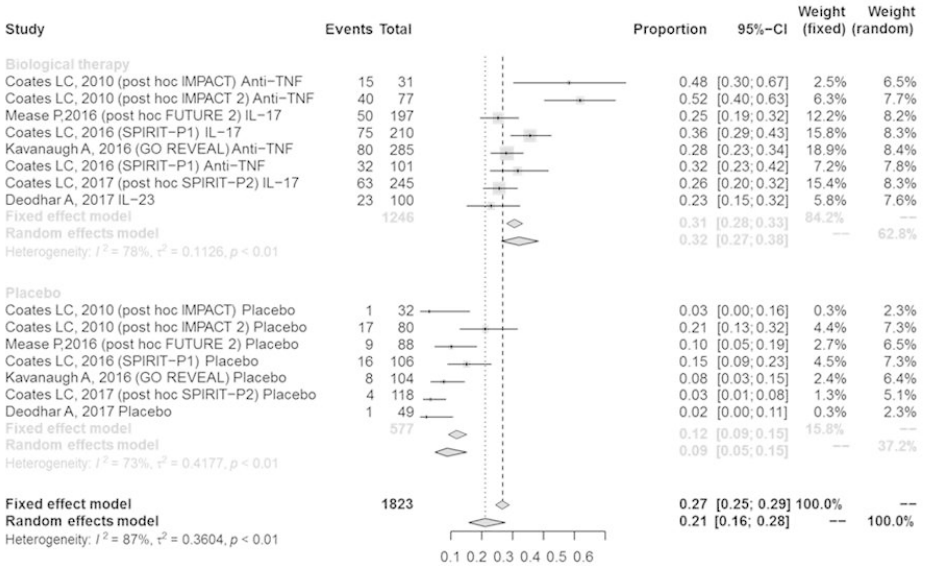

Figure 3: Prevalence of minimal disease activity in randomized clinical trials evaluating biological therapy versus placebo

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