The majority of patients with psoriatic arthritis are not eligible for randomised clinical trials

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Abstract

Objective

To identify the proportion of patients with psoriatic arthritis (PsA) who would meet inclusion criteria of the randomised clinical trials that were performed leading up to registration of the tumour necrosis factor inhibitors (TNFi).

Methods

Data from 329 patients with PsA were obtained from an Icelandic database, ICEBIO, medical records at the University Hospital of Iceland, and the private out-patient clinic Laeknasetrid Ltd. The patients were classified according to whether they met the inclusion criteria of the clinical trials that were performed ahead of the registration of each respective TNFi. The reasons for exclusion were also explored.

Results

34% of the patients with complete data available met the inclusion criteria. Clinical data in respect to exclusion and inclusion criteria were incomplete for 13% of the cases. The proportion of patients who met the inclusion criteria was highest among those who received adalimumab and etanercept (53%). Patients who received infliximab had the lowest inclusion rate (23%). The main reason why patients did not meet the inclusion criteria was too few swollen and/or tender joints, or in 45% of excluded cases.

Conclusion

Our results demonstrate that two thirds of patients with PsA in Iceland who are treated with TNFi would not have qualified for the randomised clinical trials performed leading up to the registration of the medications. Further studies with regards to whether outcomes are different between those who met the inclusion criteria and those who did not remain to be performed.

Key words

psoriatic arthritis, TNF inhibitors, randomised clinical trials, inclusion criteria.

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease associated with the skin disease psoriasis (PSO). PsA is characterised by oligo- or poly-arthritis, and may also involve the spine. Furthermore, patients suffering from PsA frequently report problems due to dactylitis and enthesitis (1, 2).

The main treatment goal in PsA is to relieve pain, reduce the number of swollen joints, prevent joint damage, and most importantly to improve quality of life. In addition, various comorbidities, *e.g.* cardiovascular disorder, metabolic disturbances, and depression or anxiety, may influence treatment decisions (3, 4). Drug therapy for PsA has been non-specific over the years, until recently. Previously treatment options from other clinically related diseases, *e.g.* rheumatoid arthritis (RA) and ankylosing spondylitis (AS), have been used (4, 5). A breakthrough occurred when conventional disease-modifying anti-rheumatic drugs (cDMARDs) were introduced, such as methotrexate (MTX) and leflunomide (6). Furthermore, glucocorticosteroids are often used in combination with cDMARDs, most frequently for intra-articular injections (7, 8). In the late 1990s, biologic DMARDs (bDMARDs) brought a change for arthritis patients (9); the arthritis could now be controlled and the treatment target was to obtain remission (10, 11). Tumour necrosis factor inhibitors (TNFi) are the main bDMARDs used in treating PsA, although other bDMARDs such as interleukin 17 inhibitors, interleukin-12/23 inhibitors and phosphodiesterase 4 inhibitor have become available more recently (3, 9). The efficacy and safety of the different TNFi in PsA have been demonstrated to be similar in several randomised controlled trials (RCTs) (12).

Clinical trials are essential for health care. However, they have various limiting factors (9, 13). Several of these factors are due to design of the study protocol, such as selection of patients, *i.e.* inclusion and exclusion criteria, and the selection of outcome measurements (13), which all influence the clinical outcome in RCTs. Therefore, it may be problematic to transfer the results of RCTs to general daily practice (14). Thus, most specialist societies, both national and international, such as the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR), have published detailed treatment guidelines on treatment issues concerning PsA and other inflammatory arthritides to improve care and standardised decision-making regarding treatment (13, 15, 16). Additional guidelines may be enacted locally, *e.g.* in Iceland, where they take into account cost and reimbursement regulations (17).

Limited information is available regarding the proportion of patients in daily routine care who would meet inclusion criteria in RCTs. Studies on the eligibility of patients commonly seen in psychiatric practice have shown that the majority of the patients (70–80%) would not meet the inclusion criteria of RCTs in this field (18-22). A single study of the eligibility of RA patients showed that most of the patients did not meet inclusion criteria in important trials comparing TNFi and cDMARDs nor trials introducing new drugs such as bDMARD agents (13). To our knowledge, no such study has been published on PsA.

The aim of the present study was to examine the proportion of patients suffering from PsA in Iceland treated with TNFi who would have met the inclusion criteria of the RCTs that are a prerequisite for the registration of the respective TNFi that they received in their first-line treatment.

Materials and methods

The study included all ICEBIO registered patients with PsA who received one of the following TNFi: adalimumab, etanercept, golimumab or infliximab, as their first-line treatment in the period from January 1, 2000 to February 4, 2016.

ICEBIO

ICEBIO is an Icelandic nationwide database on patients treated with bDMARDs for rheumatic diseases including RA, AS and PsA. The database is based on the Danish Registry for Biologic Therapies in Rheumatology,

DANBIO (23). ICEBIO started collecting data in 2007 with a bedside prospective registration at initiation of all bDMARDs, as well as annual follow-up visits. Patients that started their treatment before 2007 have been registered retrospectively in ICEBIO based on their medical records. Currently, ICEBIO covers approximately 98% of all patients treated with bDMARDs for rheumatic disorders in Iceland (24, 25). On February 4, 2016, there was information available on 1058 individuals in ICEBIO, of whom 329 individuals had been diagnosed with PsA [Information from ICEBIO].

When patients start treatment with bDMARDs in Iceland, it is obligatory to register detailed health and disease information in the ICEBIO. Standard follow-up data are then annually registered on regular visits to out-patient clinics, both at the University Hospital as well as at private clinics. Thus, ICEBIO is both a quality registry and a research tool. At annual follow-up visits, ICEBIO calculates standard disease severity scores, which helps physicians and patients get a comprehensive overview of the disease progress (25).

The following data were collected from ICEBIO: diagnosis of PsA, the year/month in which the patient began to experience joint symptoms and the year/month when the patient was diagnosed with PsA, age, gender, height, weight, the start date and the stop date of the TNFi treatment, history of cDMARD therapy, use of glucocorticosteroids, and the number of swollen joints (SJC) and tender joints (TJC). If data were not available in ICEBIO they were obtained from the patient medical records at the University Hospital of Iceland or at the private clinic Laeknasetrid Ltd. Additional data on relevant comorbidity in the context of inclusion and exclusion of the RCTs, information about a tuberculosis test (skin test and chest x-ray), rheumatoid factor, blood chemistry, history of joint replacements, previous phototherapy and medications that were not allowed according to the study protocols of the RCTs were also obtained from the patient medical records if not already found in ICEBIO. All data were anonymised before analysis.

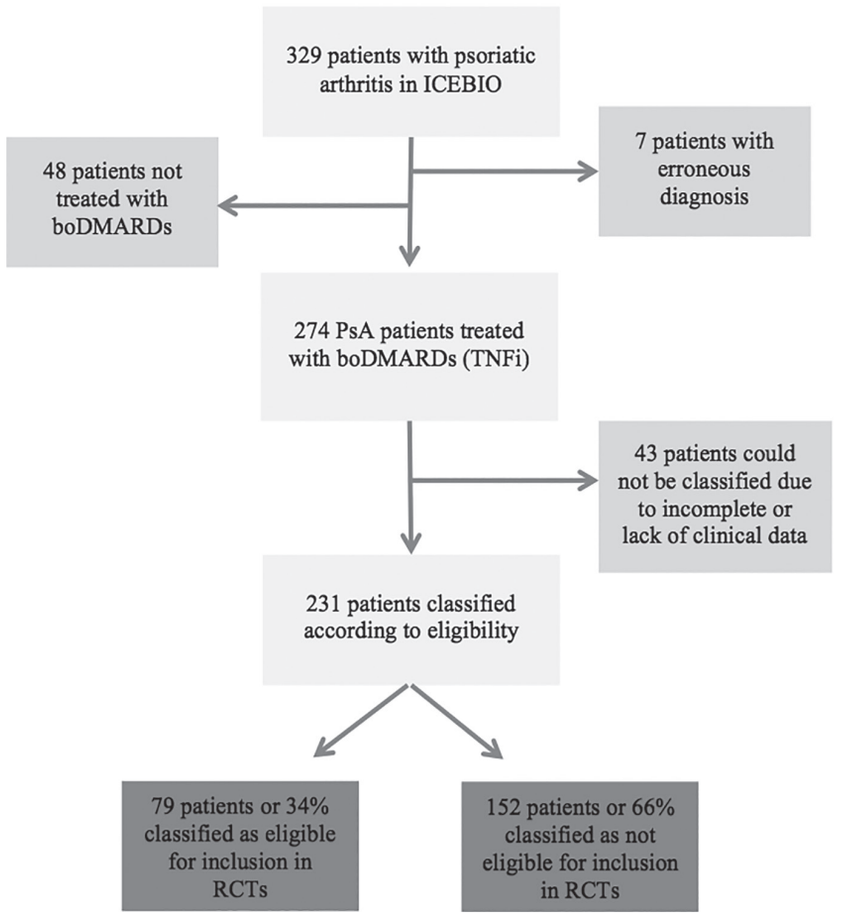

Fig. 1. Flowchart of the inclusion process and proportion of eligibility for participation in respective RCTs that were a prerequisite for the registration of the TNFi that the individual patient received.

Eligibility criteria of controlled clinical trials

The inclusion and exclusion criteria of the controlled clinical trials that are prerequisite for the registration of each of the TNFi – adalimumab, etanercept, golimumab and infliximab – were explored. A total of seven trials were studied, two each for infliximab (26, 27), etanercept (28, 29), and adalimumab (30, 31), and one regarding golimumab (32). From information obtained, each patient was classified into eligible or not eligible according to the inclusion/exclusion criteria of the respective RCTs that were conducted on the TNFi that the patient started his first-line treatment on.

Statistical analysis

Microsoft Excel® 2014 was used for statistical calculations as well as for graphical presentation of results and tables. Descriptive analysis was performed.

Ethics

The study was approved by the Icelandic National Bioethics Committee and the Icelandic Data Protection Authority (VSNb2015120017/03.03).

Results

Patients enrolled in the study

On February 4, 2016, 329 patients diagnosed with PsA were registered in ICEBIO. Seven patients had an erroneous diagnosis recorded in ICEBIO on review and 91 patients either did not receive bDMARDs or could not be classified due to incomplete or lack of clinical data. Therefore, the results are based on the remaining 231 patients who could be classified according to eligibility (Fig. 1).

Patient characteristics are presented in Table I. The majority of patients or 55% were given infliximab as a first-line treatment, 24% received etanercept, 14% golimumab, and 7% received adalimumab. The number of women

Table I. Demographics of 274 patients with psoriatic arthritis who received their first-line TNFi treatment.

Characteristics	Infliximab	Etanercept	Golimumab	Adalimumab
No. of patients (%)	151 (55)	65 (24)	39 (14)	19 (7)
Female, n (%)	82 (54)	38 (58)	23 (56)	15 (79)
Average age in years ± SD	48 ± 13.1	51 ± 12.8	47 ± 13.1	49 ± 11.6
Average weight, kg ± SD	89 ± 17.8	90 ± 17.7	91 ± 15.6	84 ± 27.8
Average height, cm ± SD	173 ± 8.5	174 ± 9.3	170 ± 3.9	171 ± 7.6
BMI, average ± SD	30 ± 5.5	31 ± 5.5	26 ± 2.2	30 ± 4.6
Duration of symptoms*	10 ± 10.6	11 ± 8.6	11 ± 11.6)	11 ± 7.9
Years since diagnosis of PsA†	7 ± 8.1	10 ± 10.0	7 ± 6.9	9 ± 6.5
Number of patients with co-morbity (%)	73 (26.6)	36 (13.1)	18 (6.6)	5 (1.8)

*Average duration in years ± SD that patients had symptoms of PsA.
†Average duration in years ± SD that patients had the diagnosis of PsA.

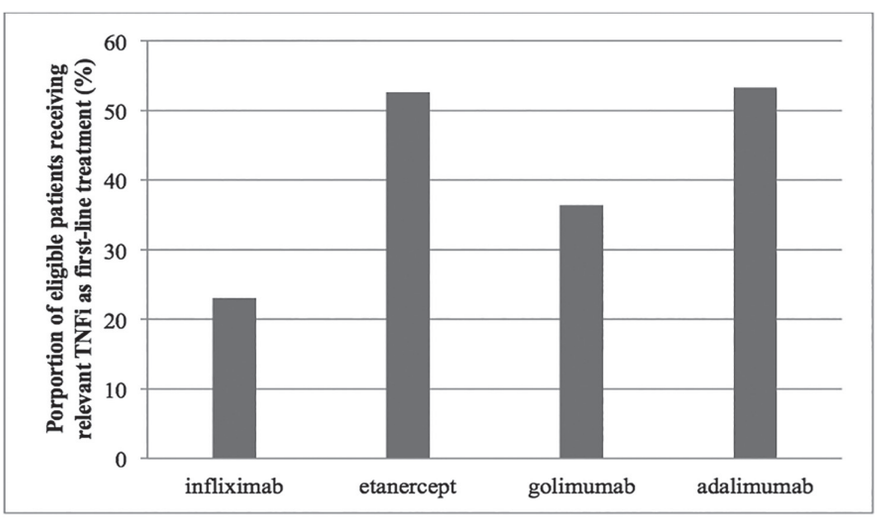

Fig. 2. Eligibility of patients for participation in the RCTs that were a prerequisite for the registration of the respective TNFi that they received in their first-line treatment.

with PsA treated with TNFi was higher than men, or 58% *versus* 42%.

Patients eligible in clinical trials

Of the 231 patients that could be classified with respect to eligibility for the respective RCTs, 79 patients would have been eligible for participation in the RCTs performed to evaluate the TNFi that they received (Fig. 1).

The proportion of patients who met the inclusion criteria was highest among those receiving adalimumab and etanercept, or 53%. Patients who received infliximab were least likely to meet trial inclusion criteria, with 23% being eligible, followed by golimumab where 36% were eligible (Fig. 2).

The main reason why patients would have been excluded from participation in the respective RCTs was an inadequate number of SJC or TJC, or in 45% of the cases (Fig. 3). Most of them or 36% were receiving infliximab. The second most frequent reason for exclusion in these RCTs, or in 16% of cases, was due to various comorbidities. Furthermore, 14% were on cDMARDs other than MTX and 7% had an inactive PSO which excluded them from participation in the adalimumab and etanercept trials. The main comorbidity reasons for excluding patients were multiple comorbidities, or in 29% of cases, followed by obesity in 13% of cases and mental health problems in another 13% of cases (Fig. 4).

Discussion

In this nationwide study inclusion and exclusion criteria of the RCTs that are a prerequisite for the registration of the TNFi adalimumab, etanercept, golimumab and infliximab were examined with the objective of exploring the eligibility of PsA patients in Iceland treated with bDMARDs in these trials. The reasons for exclusion were also examined. The present study is the first to our knowledge to explore the eligibility of PsA patients in clinical practice to be included in RCTs on bDMARDs. Our findings demonstrated that two thirds of all PsA patients in Iceland, who were treated with TNFi, would not have qualified for participation in these RCTs. Of those, 45% were excluded because they did not have an adequate number of SJC or TJC, *i.e.* they did not have a high enough level of arthritis activity. However, many PsA patients do not have polyarthritis, but rather difficult oligo- or monoarthritis, or they may only suffer from spine involvement, which excludes them from participation in the studies that we were focusing on. Furthermore, some PsA patients may mainly suffer from intense dactylitis and/or enthesitis that justify initiation of TNFi (4).

In a study exploring the proportion of RA patients that would meet the four most common criteria for inclusion in contemporary clinical trials, namely, ≥6 tender joints, ≥6 swollen joints, erythrocyte sedimentation rate (ESR) ≥28 mm/h, and early morning stiffness ≥45 minutes in two cohorts, showed that only 15% and 34% of the cohorts had ≥6 swollen and tender joints, as well as an ESR ≥28 or morning stiffness ≥45 min (33). Another study of the eligibility of the same two cohorts in two important clinical trials, the early RA (ERA) trial of methotrexate versus etanercept and the TNFi trial in RA with a concomitant therapy (ATTRACT) study of infliximab plus methotrexate versus methotrexate alone showed that only 16% and 5% of the cohorts, respectively, met the inclusion criteria (13). These studies were cross-sectional and did not consider variability of disease activity over time. A study comparing the proportion of RA patients meeting these four criteria at a single time point, over time and when starting new DMARDs or bDMARDs, showed that eligibility increased from 38% at a single time point to 68% when assessed over time and to

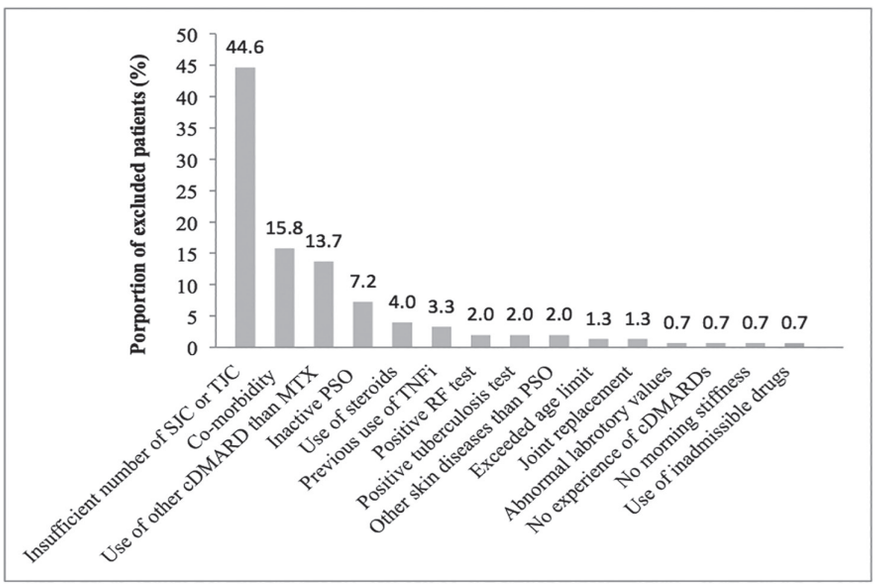

Fig. 3. The relative prevalence of exclusion reasons for patients that did not meet inclusion criterion of the RCTs.

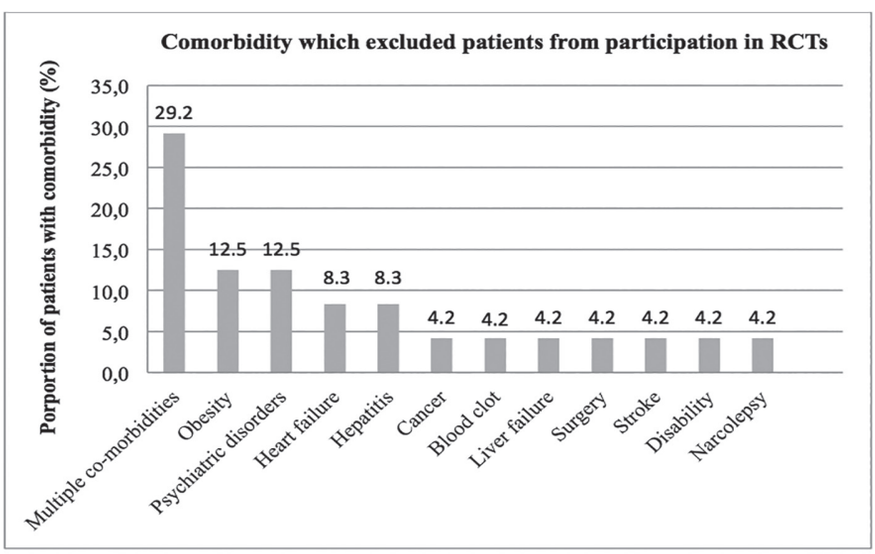

Fig. 4. The relative prevalence for certain comorbidities that excluded patients in the RCTs.

62% when starting new cDMARDs or bDMARDs (34).

Studies in other disease categories of patients' eligibility in clinical trials have shown the same trend, *e.g.* studies in the field of psychiatry revealed that around 70% of patients did not meet the inclusion criteria (18-22). It must be taken into consideration that treatments and prospects of PsA patients are of course completely different. Nevertheless, the results indicate that inclusion criteria of RCTs are strict and may exclude the majority of chronically ill patients. This raises the question of eligibility and whether it is suitable to interpret the results of such trials in relation to an entire patient population in daily clinical care.

Another finding from our study was that the patients were more likely to meet the inclusion criteria for the RCTs that are necessary for the registration of etanercept (28, 29) and adalimumab (30, 31), or in 53% cases for both drugs compared to infliximab (26, 27) where 23% of the relevant patients were ineligible in the trials. A possible explanation is that inclusion criteria in the RCTs for infliximab were at least five tender or swollen joints (26, 27) compared to at least three tender or swollen joints in the RCTs for etanercept, golimumab and adalimumab (28-32). In that study approximately two thirds of the patients on golimumab were excluded from the respective RCT. The unique thing about the inclusion criteria of the golimumab study was that participants had to have an active PSO skin disease. In this context, it is interesting that according to the recent classification criteria for psoriatic arthritis (CASPAR), which were issued prior to the golimumab study, it is not required to have PSO to be diagnosed with PsA, but instead it sufficed to have a history or family history of confirmed PSO (17).

Almost half of the patients had comorbidities. Of those who did not meet the inclusion criteria, 24 patients or 16% were excluded due to their comorbidities. The third most common reason for exclusion in our study was the use of cDMARDs other than MTX. This was a requirement in all of the RCTs except for the adalimumab study and excluded 14% of the patients.

In our study, there was a great difference in the number of patients receiving infliximab and the other three TNFi, making comparison more difficult. When a TNFi treatment is chosen for a patient in Iceland, the most cost-effective treatment at the time should be chosen according to national clinical guidelines, which are based on annual or biannual tenders. This explains the high number of patients that received infliximab (17).

One sixth of the patients had incomplete data, particularly those who started treatment before 2006, and this might have influenced the results of the study. ICEBIO contains detailed clinical information on all rheumatic patients treated with bDMARDs in Iceland; however, data in clinical registries are never fully complete as in RCTs. We assume that the same proportion of this group of patients would not be eligible for participation in RCTs, since there were no differences in general health information between those 43 patients which we were unable to classify and those who did or did not meet the inclusion criteria (data not shown). Another point of consideration was the use of combined inclu-

sion and exclusion criteria of the RCTs of infliximab (26, 27), etanercept (28, 29) and adalimumab (30, 31). Therefore, it is a possibility that patients that were excluded from one study would not have been excluded from the other one. In context, the inclusion rate in these seven studies were not provided in each study, but the inclusion rate was 62% for infliximab (26), 68% and 85% for etanercept (28, 29), 91% for adalimumab (30) and 73% for golimumab (32). Thus, at rates much higher than in our surroundings from daily clinical praxis, we found only 34% of our patients who were receiving TNFi eligible for inclusion (see Fig. 2).

In conclusion, the results of the present study demonstrate that the majority of patients with PsA in Iceland would be excluded from the RCTs that are prerequisite for the registration of the TNFi. Low swollen and tender joint counts, comorbidity and the use of cDMARD other than MTX were the main reasons for exclusion. Further studies with regards to whether outcomes would be different between those that met the inclusion criteria and those that did not remain to be performed.

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References

1. TERENZI R, MONTI S, TESEI G, CARLI L: One year in review 2017: Spondyloarthritis. *Clin Exp Rheumatol* 2018; 36: 1-14.
2. MCINNES IB: Psoriatic arthritis: embracing pathogenetic and clinical heterogeneity? *Clin Exp Rheumatol* 2016; 34 (Suppl. 98): S9-S11.
3. KAVANAUGH AF, RITCHLIN & COMMITTEE: Systematic review of treatments for psoriatic arthritis: An evidence based approach and basis for treatment guidelines. *J Rheumatol* 2006; 33: 1417-21.
4. COATES LC, KAVANAUGH A, MEASE PJ *et al*.: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol* 2016; 68: 1060-71.
5. KUEK A, HAZLEMAN BL, OSTOR AJ: Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: A medical revolution. *Postgrad Med J* 2007; 83: 251-60.
6. SMOLEN JS, VAN DER HEIJDE D, MACHOLD KP *et al*.: Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2014; 73: 3-5.
7. DONAHUE KE, GARTLEHNER G, JONAS DE *et al*.: Comparative effectiveness of drug therapy for rheumatoid arthritis and psoriatic arthritis in adults. *Rockville (MD): Agency for Healthcare Research and Quality (US)* 2007.
8. GOSSEC L, SMOLEN JS, GAUJOUX-VIALA C *et al*.: European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 2012; 71: 4-12.
9. HETLAND ML: Modern treatment strategies in rheumatoid arthritis. *Dan Med Bull* 2011; 58: B4320.
10. BOEHNCKE WH, QURESHI A, MEROLA JF *et al*.: Diagnosing and treating psoriatic arthritis: An update. *Br J Dermatol* 2014; 170: 772-86.
11. ENG G, STOLTENBERG MB, SZKUDLAREK M *et al*.: Efficacy of treatment intensification with adalimumab, etanercept and infliximab in rheumatoid arthritis: A systematic review of cohort studies with focus on dose. *Semin Arthritis Rheum* 2013; 43: 144-51.
12. ELYOUSSFI S, THOMAS BJ, CIURTIN C: Tailored treatment options for patients with psoriatic arthritis and psoriasis: Review of established and new biologic and small molecule therapies. *Rheumatol Int* 2016; 36: 603-12.
13. SOKKA T, PINCUS T: Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 313-18.
14. BUYSE ME: The case of loose inclusion criteria in clinical trials. *Acta Chir Belg* 1990; 90: 129-31.
15. CABANA MD, RAND CS, POWE NR *et al*.: Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999; 282: 1458-65.
16. GLADMAN DD, MEASE PJ: Towards international guidelines for the management of psoriatic arthritis. *J Rheumatol* 2006; 33: 1228-30.
17. Icelandic National Guidelines, http://www.landspitali/?pageid=16144&itemid=0b66c952-2d24-4bc9-bc26-2edd216bb000. 2017.
18. BLANCO C, OKUDA M, WRIGHT C *et al*.: Mental health of college students and their non-college-attending peers: results from the National Epidemiologic Study on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2008; 65: 1429-37.
19. ZIMMERMAN M, MATTIA JI, POSTERNAK MA: Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002; 159: 469-73.
20. HOERTEL N, STRAT YL, BLANCO C *et al*.: Generalizability og clinical trial results for generalized anxiety disorder to communty samples. *Wiley Online Library* 2012; 29: 614-20.
21. OKUDA M, HASIN DS, OLFSON M *et al*.: Generalizability of clinical trials for cannabis dependence to community samples. *Drug Alcohol Depend* 2010; 111: 177-81.
22. ODLAUG BL, WEINHANDL E, MANCEBO MC *et al*.: Excluding the typical patient: thirty years of pharmacotherapy efficacy trials for obsessive-compulsive disorder. *Ann Clin Psychiatry* 2014; 26: 39-46
23. HETLAND ML, KROGH NS, HØRSLEV-PETERSEN K, SCHIØTTZ-CHRISTENSEN B, SØRENSEN IJ, DORTE VENDELBO J: Using an electronic platform interactively to improve treatment outcome in patients with rheumatoid arthritis: new developments from the DANBIO registry. *Clin Exp Rheumatol* 2016; 34 (Suppl. 101): S75-S78.
24. HETLAND ML: DANBIO--powerful research database and electronic patient record. *Rheumatology* (Oxford) 2011; 50: 69-77.
25. GLINTBORG B, GUDBJORNSSON B, KROGH NS *et al*.: Impact of different infliximab dose regimens on treatment response and drug survival in 462 patients with psoriatic arthritis: results from the nationwide registries DANBIO and ICEBIO. *Rheumatology* (Oxford) 2014; 53: 2100-9.
26. ANTONI CE, KAVANAUGH A, KIRKHAM B *et al*.: (2005) Sustained Benefits of Infliximab Therapy for Dermatologic and Articular Manifestations of Psoriatic Arthritis Results From the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum* 2005; 52: 1227-36.
27. ANTONI C, KRUEGER GG, DE VLAM K *et al*.: Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005; 64: 1150-7.
28. MEASE PJ, GOFFE BS, METZ J *et al*.: Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000; 356: 385-90.
29. MEASE PJ, KIVITZ AJ, BURCH FX *et al*.: Etanercept treatment of psoriatic arthritis - Safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; 50: 2264-72.
30. MEASE PJ, GLADMAN DD, RITCHLIN CT *et al*.: Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis - Results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 3279-89.
31. GENOVESE MC, MEASE PJ, THOMSON GT *et al*.: "Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy." *J Rheumatol* 2007; 34: 1040-50.
32. KAVANAUGH A, MCINNES IB, MEASE PJ *et al*.: Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study. *Ann Rheuma Dis* 2013; 72: 1777-85.
33. SOKKA T, PINCUS T: Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. *J Rheumatol* 20003; 30: 1138-46.
34. KINGSLEY GH, KHOSHABA B, SMITH CM *et al*.: Are clinical trials in rheumatoid arthritis generalizable to routine practice? A re-evaluation of trial entry criteria. *Rheumatology* (Oxford) 2005; 44: 629-32.