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LUND UNIVERSITY | UNIVERSITY OF ICELAND

Exploring the Gap Between Clinical Trials and Real-World Practice in Psoriatic Arthritis

Ólafur Pálsson

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University and the Faculty of Medicine at the University of Iceland to be publicly defended on Friday the 13th of February at 09:00 in Ceremonial Hall, University of Iceland, Sæmundargata 2, Reykjavík, Iceland.

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Abstract: Psoriatic arthritis is a chronic, potentially disabling inflammatory joint disorder associated with psoriatic skin disease. The burden of psoriatic arthritis is often substantial and long-lasting, both for patients and for society. The treatment and follow-up of patients with psoriatic arthritis is multifaceted and may require multidisciplinary collaboration.

Most management guidelines rely heavily on results from randomised controlled pharmaceutical trials, yet only about a third of patients would be eligible to participate in these studies, which may limit their external validity. In Study I, we demonstrate that patients who would not have been eligible for clinical trials for biologic disease modifying anti-rheumatic drugs (bDMARDs) still experience comparable clinical benefits and have similar drug survival as patients who would have met the trial criteria.

Managing chronic joint pain is an important component of care in psoriatic arthritis. Non-steroidal anti-inflammatory drugs are frequently used for pain control, although they may have potentially severe side-effects. In Study II, we demonstrate that patients initiating TNF inhibitors reduce their NSAID consumption by 40-50%, highlighting an indirect safety benefit of introducing bDMARD therapy.

The optimal treatment goal in psoriatic arthritis is the resolution of all signs and symptoms of disease, a state called remission, without adverse treatment effects. Reaching and maintaining remission for longer periods of time, termed sustained remission, has been shown in rheumatoid arthritis to improve long-term outcomes through better physical function, quality of life and less radiographic progression. Sustained remission has not extensively been studied in psoriatic arthritis. In Studies III and IV, we investigate the prevalence and predictors of sustained remission in Sweden and Iceland. Despite access to advanced therapies, fewer than half of all patients ever achieved a state of remission during follow-up, and fewer than one third of patients ever achieved sustained remission. Fewer swollen joints at the start of the first bDMARD therapy predicted a greater likelihood of sustained remission.

Key words: psoriatic arthritis, biologic treatment, remission, sustained remission

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Cover image by Ólafur Pálsson. Image taken during the 2021 Fagradalsfjall volcanic eruptions

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Contents

LIST OF ABBREVIATIONS

ACR - American College of Rheumatology
ACR20/50/70 - ≥20%, ≥50%, or ≥70% improvement according to ACR response criteria
AC - Acromioclavicular (joint)
AI – Artificial Intelligence
ASDAS - Ankylosing Spondylitis Disease Activity Score
BASDAI - Bath Ankylosing Spondylitis Disease Activity Index
BASFI - Bath Ankylosing Spondylitis Functional Index
BASMI - Bath Ankylosing Spondylitis Metrology Index
bDMARD - Biologic Disease-Modifying Anti-Rheumatic Drug
BMI - Body Mass Index
BSA - Body Surface Area
CASPAR - Classification Criteria for Psoriatic Arthritis
COX - Cyclooxygenase
CRP - C-Reactive Protein
csDMARD - Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
DAPSA - Disease Activity Index for Psoriatic Arthritis
DAPSA28 - Disease Activity Index for Psoriatic Arthritis using 28-joint counts
DDD - Defined Daily Dose
DMARD - Disease-Modifying Anti-Rheumatic Drug
EGA - Evaluator's Global Assessment
EQ-5D - EuroQol 5-Dimension Health Questionnaire
ESR - Erythrocyte Sedimentation Rate
EULAR - European Alliance of Associations for Rheumatology
GRACE - Group for Research and Assessment in Psoriasis and Psoriatic Arthritis Composite Score
GRAPPA - Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ - Health Assessment Questionnaire
HAQ-DI - Health Assessment Questionnaire Disability Index
HLA - Human Leukocyte Antigen
ICEBIO - Icelandic Biologic Registry
IL - Interleukin
IPMR - Icelandic Prescription Medicines Register (Lyfjagagnagrunnur Landlæknis)
JAK - Janus Kinase
LUNDEX - Lund Efficacy Index
MCAR - Missing Completely At Random

MCP - Metacarpophalangeal (joint)
MDA - Minimal Disease Activity
MHC - Major Histocompatibility Complex
MNAR - Missing Not At Random
MTP - Metatarsophalangeal (joint)
NSAID - Non-Steroidal Anti-Inflammatory Drug
OMERACT - Outcome Measures in Rheumatology
PASI - Psoriasis Area and Severity Index
PASDAS - Psoriatic Arthritis Disease Activity Score
PDE4i - Phosphodiesterase-4 inhibitor
PIP - Proximal Interphalangeal (joint)
PRO - Patient Reported Outcome
PsA - Psoriatic Arthritis
PsARC - Psoriatic Arthritis Response Criteria
RA - Rheumatoid Arthritis
RCT - Randomised Controlled Trial
RR - Relative Risk
SF-36 - Short-Form 36 Health Survey
SJC - Swollen Joint Count
SJC28 - 28-joint Swollen Joint Count
SR - Sustained Remission
SRQ - Swedish Rheumatology Quality Register
TJC - Tender Joint Count
TNF - Tumour Necrosis Factor α
TNFi - Tumour Necrosis Factor inhibitor
TMJ - Temporomandibular Joint
ToPAS - Toronto Psoriatic Arthritis Screen
tsDMARD - Targeted Synthetic Disease-Modifying Anti-Rheumatic Drug
VAS - Visual Analogue Scale
VLDA - Very Low Disease Activity

1 – INTRODUCTION

“Clinicians may all too easily spend years writing ‘doing well’ in the notes of a patient who has become progressively crippled before their eyes"

- Verna Wright

This thesis explores the gap between clinical trials and real-world practice in the management of established arthritis, particularly psoriatic arthritis. Psoriatic arthritis is a chronic, life-long disease and in evidence-based management we often rely heavily on results from randomised clinical trials (RCTs) conducted over a limited period of time. When following patients over many years, or even decades we often do not have definitive answers to common clinical scenarios. Despite substantial advances in therapy, there remains a significant gap between the efficacy demonstrated in RCTs and the effectiveness achieved in everyday clinical practice. This thesis aims to explore this gap and investigates:

- Whether patients with psoriatic arthritis who do not fulfil the inclusion criteria for RCTs achieve equal benefits from medical therapy.
- Whether total NSAID use is affected by biologic disease-modifying therapy.
- The prevalence and predictors of longer-term sustained remission in Sweden.
- The prevalence of sustained remission in Iceland, a comparison with Sweden, and what we might learn from the differences.

List of papers

This thesis is based on the following studies, which are referred to by their Roman numerals in the text.

I. **Palsson O**, Love TJ, Gunnarsdottir AI, Gunnarsson PS, Runarsdottir EE, Krogh NS, Gudbjornsson B. *Patients with psoriatic arthritis who are not eligible for randomised controlled trials for TNF inhibitors have treatment response and drug survival similar to those who are eligible.* RMD Open. 2019 Jul 16;5(2):e000984. doi: 10.1136/rmdopen-2019-000984. PMID: 31413869; PMCID: PMC6667974.

II. **Palsson O**, Love TJ, Wallman JK, Kapetanovic MC, Gunnarsson PS, Gudbjornsson B. *Prescription of non-steroidal anti-inflammatory drugs for patients with inflammatory arthritis decreases with the initiation of tumour necrosis factor inhibitor therapy: results from the ICEBIO registry.* Scand J Rheumatol. 2024 Nov;53(6):402-408. doi: 10.1080/03009742.2024.2352967. Epub 2024 Jun 4. PMID: 38832494.

III. **Palsson O**, Einarsson JT, Wallman JK, Love TJ, Gudbjornsson B, Kapetanovic MC. *Prevalence and Predictors of Achieving Sustained Remission in Psoriatic Arthritis: A Swedish Nationwide Registry Study.* J Rheumatol. 2025 Oct 1;52(10):997-1004. doi: 10.3899/jrheum.2024-1250. PMID: 40374512.

IV. **Palsson O**, Einarsson JT, Wallman JK, Love TJ, Gudbjornsson B, Kapetanovic MC. *Sustained Remission in Psoriatic Arthritis Patients Using Biologics in Iceland and Sweden. A Comparative Study of Two National Registries. Manuscript.*

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Lay summary

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease that occurs in some people who have the skin condition psoriasis. The disease can cause pain, swelling, stiffness and progressive joint damage, as well as fatigue and reduced quality of life. The condition varies greatly: some patients experience only mild joint inflammation, while others develop severe arthritis leading to joint destruction and permanent disability. PsA can also affect the tendons, the spine, and the skin, and is associated with other health problems such as obesity, depression and cardiovascular disease.

In recent decades, biologic and targeted synthetic drugs have revolutionised PsA treatment. These medications target specific components of the immune system and can thereby reduce inflammation and prevent joint damage. They have made remission – a state without signs or symptoms of disease – an attainable goal for many patients.

However, most of the knowledge about the effects of biologic treatments comes from randomised controlled trials (RCTs), which include carefully selected participants and follow them for a relatively short period of time. As a result, it is not always clear how well these treatments work in the broader and more diverse population of patients seen in rheumatology clinics, such as older patients or those with other chronic conditions.

The overall aim of this thesis was to explore the gap between clinical trials and real-world practice in PsA. Using nationwide rheumatology registries from Iceland (ICEBIO) and Sweden (SRQ), the studies examined how effective biologic and targeted synthetic therapies are when used in routine care, and how often patients achieve sustained remission – meaning long-term disease control.

The first study compared patients in Iceland who met the strict inclusion criteria used in RCTs for biologic drugs with those who would have been excluded. Two-thirds of real-world patients would not have qualified for the trials, mainly because of milder joint inflammation or coexisting health conditions. Nevertheless, their treatment response and drug persistence were similar to those of RCT-eligible patients, indicating that the benefits of biologic therapy extend to a broader group than those investigated in the RCTs.

The second study linked registry data with a national prescription database in Iceland and showed that initiating biologic therapy reduced the consumption of non-steroidal anti-inflammatory drugs (NSAIDs) by 40-

50%. This suggests improved inflammatory control and reduces the need for NSAIDs which may have side effects such as stomach ulcers, heart or kidney disease.

The third and fourth studies investigated the frequency of sustained remission, or the ability to keep inflammation under control for an extended period. About one in four patients achieved sustained remission based on objective measures and only half of the patients ever experienced remission at least once. Male sex and fewer swollen joints at the start of treatment predicted better outcomes. These results highlight the benefits of biologic and targeted synthetic therapies, but also the ongoing challenge of maintaining long-term disease control.

In summary, this thesis shows that the benefits of biologic therapy extend beyond narrowly defined trial populations, that effective disease control reduces the need for NSAIDs, and that sustained remission remains an important but challenging goal. Continued registry-based research will help refine treatment strategies, guide personalised care, and ensure that advances in therapy translate into genuine, long-term improvements for all people living with PsA.

Vísindamiðlun

Sóragigt er langvinnur liðbólgusjúkdómur sem leggst á hluta sjúklinga sem hafa húðsjúkdóminn psoriasis. Sjúkdómurinn veldur verkjum, bólgu, stirðleika og skemmdum í liðum ásamt þreytu og skertum lífsgæðum. Einkenni og alvarleiki sóragigtar eru afar misjöfn meðal sjúklinga, sumir hafa einungis væg einkenni í fáum liðum meðan aðrir fá hraðágengar og útbreiddar liðskemmdir. Sóragigt getur einnig lagst á hryggsúluna, sinar, sinafestur, húð og neglur og tengist oft öðrum sjúkdómum eins og offitu, þunglyndi og hjarta- og æðasjúkdómum. Á undanförnum áratugum hafa líftæknilyf orðið sífellt aðgengilegri og þau hafa gjörbreytt horfum sjúklinga með sóragigt. Slík lyf bremsa ákveðnar boðleiðir í ónæmiskerfinu og minnka þannig bólguvirkni til að koma í veg fyrir liðskemmdir. Þau hafa gert það að verkum að sjúkdómshlé – ástand þar sem sjúklingur hefur engin einkenni né ummerki um sjúkdóm, hafa orðið að mögulegu markmiði meðferðar.

Þekking okkar á virkni líftæknilyfja kemur að mestu leyti úr tvíblindum slembiröðuðum rannsóknum, sem velja sjúklinga vandlega inn í rannsóknina og fylgja þeim eftir í stuttan tíma. Vegna þessa er ekki alltaf ljóst hversu vel þessi lyf virka hjá þeim sjúklingum sem við hittum á göngudeildum gigtarsjúkdóma.

Markmið þessarar doktorsritgerðar var að kanna bilið milli niðurstaðna tvíblindra slembiraðaðra rannsókna og raunverulegra aðstæðna í klínísku starfi við sóragigt. Gagnabankar eru stöðluð verkfæri sem notuð eru í flestum löndum til að fylgja eftir sjúklingum á líftæknilyfjameðferð. Slíkir gagnabankar safna kerfisbundið upplýsingum um gigtarsjúkdóma og meðferðarsvörun. Gagnabankarnir sem eru í notkun á Íslandi (ICEBIO) og í Svíþjóð (SRQ) innihalda upplýsingar um nær alla sjúklinga með sóragigt sem fá líftæknilyfjameðferð. Með því að skoða þessa gagnabanka getum við rannsakað virkni líftæknilyfjanna þegar þeim er beitt í klínísku starfi og hversu oft sjúklingar ná langtíma eða viðvarandi sjúkdómshlé.

Fyrsta rannsóknin bar saman sjúklinga á Íslandi sem hefðu uppfyllt ströng inntökuskilyrði tvíblindra slembiraðaðra rannsókna og þá sem ekki hefðu uppfyllt inntökuskilyrðin. Tveir þriðju hlutar sjúklinganna hefðu ekki komist inn í tvíblindu rannsóknirnar, aðallega þar sem þeir höfðu færri bólgna liði eða aðra undirliggjandi sjúkdóma. Þrátt fyrir það höfðu þeir álíkan árangur af líftæknilyfjameðferð og voru jafn lengi á lyfjunum og þeir sem hefðu komist inn í rannsóknirnar. Það gefur til kynna að niðurstöður tvíblindra slembiraðaðra rannsókna megi heimfæra á stærri hóp en þann sem getur tekið þátt í tvíblindum rannsóknum.

Önnur rannsóknin tengdi saman Lyfjagagnagrunn Landlæknis og ICEBIO og sýndi að við upphaf líftæknilyfjameðferðar helmingaðist notkun bólgueyðandi gigtarlyfja (NSAID). Þetta gefur til kynna betri stjórn á bólgu af völdum sjúkdómsins og dregur úr líkum á mögulega hættulegum aukaverkunum bólgueyðandi gigtarlyfja.

Þriðja og fjórða rannsóknin skoðuðu viðvarandi sjúkdómshlé eða möguleikann á því að halda bólgu niðri yfir lengri tíma. Einungis fjórðungur sjúklinga komst í viðvarandi sjúkdómshlé og tæplega helmingur upplifðu sjúkdómshlé á einhverjum tímapunkti. Karlkyn og færri bólgnir liðir við upphaf meðferðar spáðu fyrir um betri svörun.

Saman sýna þessar rannsóknir að líftæknilyfjameðferðir eru öflugar og gagnlegar í þessum sjúklingahópi og að áhrifin ná einnig til þeirra sem ekki uppfylla inntökuskilyrði slembirannsókna. Þrátt fyrir líftæknilyfjameðferð þurfa margir enn bólgueyðandi gigtarlyf til að halda einkennum í skefjum. Þó svo að nú sé raunhæft að stefna að sjúkdómshléi hjá öllum sjúklingum er þörf á betri meðferðarferlum til að fleiri sjúklingar nái viðvarandi sjúkdómshléi.

Populärvetenskaplig sammanfattning

Psoriasisartrit (PsA) är en kronisk inflammatorisk ledsjukdom som drabbar vissa med hudsjukdomen psoriasis. Sjukdomen orsakar smärta, svullnad och stelhet i leder, trötthet och försämrad livskvalitet. Symtomen varierar mycket mellan olika individer, vissa har en lindrig sjukdom i ett fåtal leder medan andra utvecklar uttalade ledskador och funktionsnedsättning. PsA kan även påverka ryggraden, senfästen och hud, och är ofta kopplad till andra sjukdomar, som övervikt, depression och hjärt-kärlsjukdom. Under de senaste decennierna har biologiska läkemedel blivit mer tillgängliga och kraftigt förändrat behandlingsmöjligheterna. Dessa läkemedel kan dämpa vissa delar av immunsystemet och på det viset minska inflammation och stoppa ledskador. Nu har remission – ett tillstånd utan symtom eller tecken på sjukdom blivit ett realistiskt behandlingsmål.

Kunskapen kring biologiska läkemedel kommer framför allt från randomiserade studier, som har strikta inklusionskriterier och vanligtvis endast följer patienter under en kort period. Därför är det inte helt klart hur väl dessa behandlingar fungerar i den patientpopulation som ses på reumatologiska mottagningar.

Målet med denna avhandling är att undersöka luckan mellan randomiserade studier och verkligheten i vården av PsA. Reumatologiregistren på Island (ICEBIO) och i Sverige (SRQ) innehåller information om nästan alla med biologisk behandling för PsA. Data från dessa register används för att undersöka effekten av biologiska behandlingar när de används i klinisk praxis och hur ofta patienter uppnår långvarig remission.

Den första studien undersökte patienter från Island som inte skulle ha inkluderats i randomiserade studier och jämförde dem med patienter som skulle uppfylla inklusionskriterierna. Studien visade att två tredjedelar av patienter som fick biologiska läkemedel på Island skulle inte ha uppfyllt inklusionskriterierna, främst på grund av mildare sjukdom eller samsjuklighet. Trots detta fick patienter som inte skulle ha inkluderats i randomiserade studier lika god effekt av läkemedlen och ändrade sin behandling lika ofta som patienter som skulle ha inkluderats.

Den andra studien undersökte användningen av antiinflammatoriska smärtstillande läkemedel (NSAIDs) före och efter insättning av biologisk behandling. Genom att koppla data från ICEBIO med det isländska receptregistret kan man se att patienter med inflammatoriska ledsjukdomar använde betydligt mer NSAID än övriga befolkningen. Efter behandlingsstart minskade användningen med 40-50%. Detta återspeglar

bättre kontroll av inflammationen och lägre risk för potentiellt allvarliga biverkningar som magsår, njurskador och försämrad hjärt-kärlsjukdom.

Den tredje och fjärde studien fokuserade på remission och långvarig remission. Många patienter förbättrades under behandling med biologiska läkemedel, men endast en fjärdedel uppnådde långvarig remission och nästan hälften upplevde aldrig remission. Män och patienter med färre svullna leder vid behandlingsstart hade större sannolikhet att uppnå långvarig remission. Dessa resultat visar att långvarig remission är möjlig men fortfarande en utmaning att uppnå.

Sammantaget visar avhandlingen att biologisk behandling har god effekt i klinisk praxis, även hos patienter som ofta utesluts från studier. Den understryker värdet av nationella reumatologiregister och visar att biologisk behandling ger nytta utöver minskad inflammation genom ett minskat NSAID-behov. Långvarig remission är ett realistiskt men krävande mål. Fortsatt forskning kommer med all sannolikhet att så småningom bidra till en mer personcentrerad behandling och säkerställa en verklig förbättring för alla patienter med PsA.

Statement on the use of artificial intelligence.

Generative artificial intelligence model ChatGPT-5 (AI, OpenAI, San Francisco, CA, USA) was partly used as writing assistance in construction of this thesis. It was employed to assist in modelling the initial structure of the thesis, summarizing references and resolving writer's block. AI was used to assist with language formulation and text editing, all interpretations are provided entirely by the author. No AI generated text, data or citations were used without critical review and verification. No research data were made available to the AI model except the final results already published in Studies I-III.

The use of AI adhered to the Lund University Faculty of Medicine guidelines for transparency and academic integrity in thesis writing as well as the requirements of the University of Iceland. I have personally written every sentence of this thesis, verified every reference and take full responsibility for the accuracy, interpretation and originality of its content.

2 – PSORIATIC ARTHRITIS

Background

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory arthritis that is associated with the skin disease psoriasis. Psoriasis affects around 3-6% of the population, of whom 18.5-20.9% also have PsA.[1-4] It is characterised by a wide variety of presentations, including peripheral arthritis, enthesitis, dactylitis, axial disease and skin or nail psoriasis.[5] It carries a substantial disease burden, including risks of functional disability, work disability and impaired quality of life. In addition, PsA is associated with the metabolic syndrome and increased cardiovascular risk.[6, 7]

In the early years of treating PsA there were few therapeutic options. Most therapies were aimed to alleviate the symptoms of disease. These included non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid injections for inflamed joints, enthesitis and dactylitis. These treatments are still used in patients with mild disease or as a complement to more efficacious treatments.[8, 9] The disease-modifyng anti-rheumatic drugs (DMARDs) are the agents shown to prevent or slow down the accrual of joint damage and functional impairment, halting disease progress. Conventional synthetic DMARDs (csDMARDs) such as methotrexate, sulfasalazine and leflunomide (and previously cyclosporin A) are still the cornerstone of therapy, but there is an inadequate response in a many of patients.

Around the turn of the century, biologic DMARDs (bDMARDs) were introduced, initially inhibitors of tumour necrosis factor α (TNF), and subsequently inhibitors of several other pro-inflammatory cytokines. More recently, targeted synthetic DMARDs (tsDMARDs) have emerged and further expanded the medical armamentarium. Over the past three decades, there has been a significant shift in the management of inflammatory arthritis including PsA. With a multitude of available drugs to treat PsA, the focus is increasingly shifting toward optimal management and individualized care. Remission, a state without signs or symptoms of disease, or low disease activity in all patients has become a treatment goal. This strategy (treat-to-target or T2T) is endorsed by both the European Alliance of Associations for Rheumatology (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidelines.[8, 9] PsA remains an incurable life-long disease, the achievement of these targets should remain a long-term goal, and staying in

remission for extended periods, years rather than months, should be the preferred goal.

Introduction

PsA is a chronic immune-mediated inflammatory arthritis that belongs to the group of spondyloarthritis.[10] It is associated with either skin psoriasis or a family history of the disease. PsA is characterized by inflammation of the joint synovium as well as inflammation of tendon and ligament insertion sites (enthesitis) and can occur both in peripheral and axial joints.[11] PsA shares immunopathogenesis with psoriatic skin disease, and the manifestations overlap other spondyloarthritis, such as the axial involvement and enthesopathy in ankylosing spondylitis, or asymmetrical large joint inflammation seen in peripheral spondyloarthritis.

Historically, PsA was considered a more benign form of rheumatoid arthritis (RA), but it was later found that it can be progressive, destructive, and disabling if left untreated.[12] Structural joint damage, functional decline and reduced quality of life occur in a substantial portion of patients.[13] Although PsA is often not rapidly destructive, in some cases, it can cause severe disability within the first few years of diagnosis. Significant diagnostic delays are common, and a delay of six months has been shown to affect long-term joint damage and functional disability.[14] PsA is associated with the metabolic syndrome in up to 40% of patients and, in addition to the musculoskeletal manifestations, chronic systemic inflammatory activity contributes to increased cardiovascular morbidity.[6, 15]

Epidemiology

PsA is a relatively common chronic inflammatory disease that affects men and women equally. Skin psoriasis is a common disease and according to a 2017 systematic review has been reported to affect between 0.51% to 11.43% of the general population.[16] Approximately 19.7% (95% CI, 18.5%-20.9%) of patients with psoriasis have PsA, with prevalence varying between regions, being more common in European patients and less common in Asian patients.[4] The incidence of PsA among patients with psoriasis ranged from 0.27 to 2.7 per 100 person-years.[4] Psoriasis scalp lesions, nail dystrophy and intergluteal/perianal lesions were associated with a higher risk of PsA.[17] The severity and activity of skin psoriasis has only a modest correlation to the activity of PsA.[18] The prevalence and incidence rates of PsA in the general population were estimated 133 and 83 cases per 100,000 person-years, respectively.[3] In the majority of patients

with PsA, psoriasis precedes the onset of arthritis, with a median time of 7 to 8 years, but the arthritis can precede the skin disease in 7-15% of patients.[19]

In Sweden, the mean annual incidence of clinically diagnosed PsA in 2014-2016 is 15-83/100,000 person-years. Incidence was slightly higher in females, lower in individuals with higher education and peaked between 50-59 years of age.[20]

In Iceland, the prevalence, demographics and disease course were described in 2007.[21] The prevalence of PsA in the adult population was estimated at 139 per 100,000 (95% CI 112-169) or 0.14% at that time. While the prevalence is likely higher today, due to increased diagnostic awareness and better access to rheumatologic evaluation, PsA was strikingly more common in women with a nearly 2:1 ratio.

Pathogenesis

The pathogenesis of PsA is complex and the disease may exhibit bone and joint changes typical of other arthritides.[22] It may feature inflammatory back pain and dactylitis similar to spondyloarthritis, but may even present similarly to RA. The pathogenesis is likely closely related to that of psoriatic skin disease. PsA patients display familial clustering, environmental associations and altered gut microbiomes.[23, 24] PsA may occur after mechanical stress or trauma at the insertion of the enthesis.

Genetic factors

A study on the heritability of PsA in Reykjavík, Iceland was conducted in 2009, following the previously mentioned prevalence study. Patients with PsA were found to be significantly more related to each other than randomly sampled subjects. In addition, first-degree relatives of patients with PsA had a relative risk (RR) of 39 to be affected by PsA. Second-degree relatives had a RR of 12.2 and the risk extended to fourth-degree relatives with an RR of 2.6.[25]

Genome-wide association studies indicate that PsA is a highly heritable disorder, which is facilitated by multiple genes of low or modest effect size.[26] While multiple genes have been demonstrated to be linked to psoriasis, fewer have been found to be linked specifically with PsA. The proteins encoded by the susceptibility loci for psoriasis and possibly PsA are both in the major histocompatibility complex (MHC), and various other genes which often affect the immune system. Specific MHC alleles linked to psoriasis and PsA are human leukocyte antigen (HLA) class I genes

within the MHC on chromosome 6, particularly HLA-C*0602. There are two specific genetic risk loci that differentiate PsA from psoriasis that are now well-established, IL23R and amino acids in HLA-B.[27]

Environmental associations

Environmental and lifestyle factors also modify the risk of PsA. Obesity and metabolic syndrome are consistent risk factors for PsA, possibly through higher levels of pro-inflammatory cytokines in patients with obesity.[28] Patients with PsA who are obese are less likely to achieve minimal disease activity (MDA) and respond worse to medical therapy. Weight reduction has been shown to improve PsA disease activity.[28, 29] Physical trauma can induce skin lesions of psoriasis (the Koebner phenomenon) and physical trauma has been associated with the onset of PsA (the "deep Koebner phenomenon").[30-32] Smoking is positively associated with PsA risk in the general population, but negatively associated among patients with psoriasis.[33]

Immune mechanisms

The enthesis, the junction where tendons or ligaments insert into bones, is recognized as a key anatomical site in PsA pathogenesis. Mechanical stress may trigger activation of local pro-inflammatory states, activating macrophages and dendritic cells, leading to cytokine release and recruitment of adaptive immune cells. Activated dendritic cells produce IL-23 and TNF, which are mediators of synovial inflammation, osteoclast activation, and this mechanism may link articular and skin disease.[34]

Clinical manifestations

Although the presentation of PsA is highly variable, some features may help distinguish the disease from other inflammatory joint disorders. The first, still widely taught criteria are the Moll & Wright classification criteria of 1973, which describe five subtypes of disease.[5] Although these subtypes may overlap or patients may change subtype during their disease course, they can be helpful in distinguishing PsA from other types of arthritis. These subtypes are:

1. Oligoarticular asymmetrical pattern, preferentially affecting larger joints.
2. Polyarticular symmetrical pattern, with similar joint distribution as in RA.
3. Predominantly distal interphalangeal joint involvement, often with significant psoriatic nail disease.

4. Arthritis mutilans, a rapidly progressive form with severe joint destructions.
5. Axial pattern, similar to ankylosing spondylitis.

Further, the disease can be recognised by the various domains it affects, and again multiple domains may, and do often coexist in each patient. These domains are:

1. Peripheral arthritis
2. Axial disease
3. Enthesitis, inflammation at the tendon or ligament insertion site
4. Dactylitis, inflammation of a whole digit of the hand or foot
5. Psoriasis skin disease
6. Psoriasis nail disease

In addition, there are often associated conditions that need to be taken into account, such as inflammatory bowel disease or uveitis, an inflammation of the vascular layer of the eyes.[9]

Diagnosis

The clinical heterogeneity of PsA may pose a challenge for both diagnosis and treatment. There are currently no available diagnostic criteria, and the diagnosis of PsA is primarily clinical, supported by characteristic patterns of musculoskeletal and skin involvement as well as exclusion of alternative causes of inflammatory arthritis. Key information from the medical history includes the patient's or a close relative history of psoriasis or PsA, joint pain with inflammatory characteristics and morning stiffness.[35] In PsA, typical examination findings include often asymmetrical peripheral arthritis, dactylitis (a sausage-like swelling of an entire digit), enthesitis or tenderness at tendon or ligament insertion sites, reduced spinal mobility indicating axial involvement and skin psoriasis. During examination, one should pay close attention to the nails, looking for nail pitting, subungual hyperkeratosis, onycholysis, nail crumbling, hyperkeratosis, leukonychia and oil-drop discoloration.[36]

A number of screening questionnaires have been developed to identify patients with PsA in dermatology clinics, such as the Psoriasis Epidemiology Screening Tool.[37] Additionally, the Toronto Psoriatic Arthritis Screen (ToPAS 1 and 2) was developed to identify patients with PsA in general practice.[38, 39]

Although PsA is a clinical diagnosis, classification criteria for research trials may aid in research and teaching. The most widely used criteria are the Classification Criteria for Psoriatic Arthritis (CASPAR), introduced in 2006.[40] The CASPAR criteria have an entry criterion of inflammatory

articular disease (joint, spinal or entheseal) plus at least three points from the following table (Table 1).[41]

Entry criteria: Inflammatory articular disease of the joints, spine or entheses	
Classification criteria	Points
Psoriasis Current psoriasis judged by a rheumatologist or dermatologist Personal history Family history (first- or second-degree relative)	 2 points 1 point 1 point
Nail dystrophy typical of psoriasis (onycholysis, pitting, hyperkeratosis) on current physical examination	1 point
Negative rheumatoid factor (any method except latex)	1 point
Dactylitis (current, or historical if recorded by a rheumatologist)	1 point
Juxta-articular new bone formation (ill-defined ossification near joint margins but excluding osteophytes) on plain radiographs of hands and feet	1 point
A classification of psoriatic arthritis is met if the final score equals to or exceeds 3 points. Specificity equals 98.7% and sensitivity equals 91.4% against the gold standard, which is a diagnosis established by the rheumatologist.	

Table 1: CASPAR classification criteria for PsA.

Course of PsA

The natural course of PsA is highly variable. Some patients experience mild or intermittent arthritis with symptom-free intervals in between, while others develop a disease with a chronic progressive course which can lead to joint destructions, disability and decreased quality of life.[12, 13] Joint damage in PsA has been shown to be predicted by high baseline acute phase response (CRP or ESR) and high baseline number of swollen joints.[42] While the disease most often develops over years to decades, a rapidly progressive, treatment refractory subtype called arthritis mutilans may evolve, causing rapid and severe joint destructions.[43, 44] While most patients can be categorized into subtypes as described above, the disease may change its nature during the course of the disease, most commonly from oligo- to polyarthritis or vice versa.[2] Skin and nail disease flares can occur independently of joint flares, and uveitis and inflammatory bowel disease may emerge at any point during the disease course.[45] The effects of cardiovascular disease, obesity, and metabolic syndrome may accrue over time, leading to increased morbidity.

Flares represent disease worsening and can be patient reported or be indicated by an increase in composite disease activity scores.[46] Flares in RA are associated with damage progression and disability.[47] In PsA, flares are commonly reported by patients but have not been well studied.[48] In Studies III and IV on sustained remission, we account for factors that may temporarily increase recorded disease activity but do not lead to a change in management, such as an elevated CRP during a concomitant infection.

PsA has in some studies been associated with an elevated mortality, although studies have provided inconsistent results. Increased disease activity and presence of comorbidities such as heart disease or obesity are associated with higher mortality in the PsA population.[49, 50] Young patients with PsA have been reported to be at increased mortality risk.[51] A 2023 meta-analysis of 10 studies showed no increased mortality compared to the general population.[52]

Disease activity

Markers of disease activity

According to the European Alliance of Associations for Rheumatology (EULAR), the primary goal of treating patients with PsA is to maximise health-related quality of life, through control of symptoms, prevention of structural damage, normalisation of function and social participation; abrogation of inflammation is an important component to achieve these goals.[8] Assessment of patients with PsA requires the consideration of all disease domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis, psoriatic nail disease, uveitis and IBD. The impact of disease on pain, function, quality of life and structural damage should be evaluated. Comorbidities and related conditions should also be taken into account.[9] Measuring inflammation levels can be challenging due to the heterogeneity of PsA and its predominantly seronegative nature. Laboratory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may be within the normal range even in highly active disease. We rely on various indirect indicators of active disease and multiple composite scores, each with its own strengths and limitations.

The Outcome Measures in Rheumatology (OMERACT) working group recommends that core domain sets be included in all randomised controlled trials.[53] It provides an overview of different disease activity indicators. For PsA it lists patient reported outcomes (PRO) such as pain, fatigue and

global assessment of disease activity, all reported by the patient, each on a 10cm visual analogue scale (VAS).

Musculoskeletal signs include swollen and tender joints, most commonly reported as joint counts (SJC/TJC) for specified sets of joints, usually 28 joints (metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, wrists, elbows, shoulders and knees) or 66/68 joints (the same as 28 joints in addition to distal interphalangeal (DIP), temporomandibular joints (TMJ), sternoclavicular (SC) and acromioclavicular (AC) joints, hips, ankles, tarsus/midfoot, metatarsophalangeal (MTP) joints and toe PIP joints)(Appendix).[54] Since the hip joints cannot be evaluated for swelling clinically, more joints are evaluated for tenderness in the latter set. Joint swelling is a soft tissue swelling detectable along the joint margin and fluctuation on examination is a key feature.[55] Bony enlargement and deformities are thus not counted as swollen joints. Dactylitis is usually represented by a count of 0-20 of how many fingers or toes are uniformly swollen, although in RCTs the Leeds Dactylitis Index may be used, a more formal measurement that captures the degree of swelling and tenderness as well.[56] Dactylitis differs from swollen joints in that the inflammation is not limited to the synovium but to other structures of the fingers as well, such as ligaments and tendons. Thus, one dactylitis of a finger usually includes three swollen joints (MCP, PIP and DIP). Enthesitis is often challenging to evaluate clinically, it is often evaluated by tenderness or swelling over an enthesis, but enthesitis may be painless, and in cases of bilateral enthesitis swelling can be challenging to evaluate objectively. Different scores for enthesitis have been used in trials. The Leeds Enthesitis Index, which measures tenderness at the lateral epicondyle of the elbow, medial femoral condyle, and Achilles tendon insertion bilaterally, is the most commonly used enthesitis index in PsA.[57]

The activity in skin psoriasis is typically reported as either Body Surface Area (BSA), which is the percentage of the skin affected by psoriasis, or the Psoriasis Area Severity Index (PASI), which additionally assesses erythema, induration and desquamation of psoriatic plaques.[58] The skin is divided into four sections and weighted according to the percentage of the total skin area, head (10%), arms (20%), trunk (30%), and legs (40%). Each area is scored for erythema, induration and desquamation as described in Figure 1, then the sum of the scores is multiplied by the respective skin weight. Nail psoriasis may be reported by the Nail Psoriasis Severity Index (NAPSI) which scores each nail and nail bed separately for pitting, leukonychia, red spots in the lunula, nail plate crumbling, onycholysis, splinter haemorrhages, oil drop discoloration and nail bed hyperkeratosis.[59]

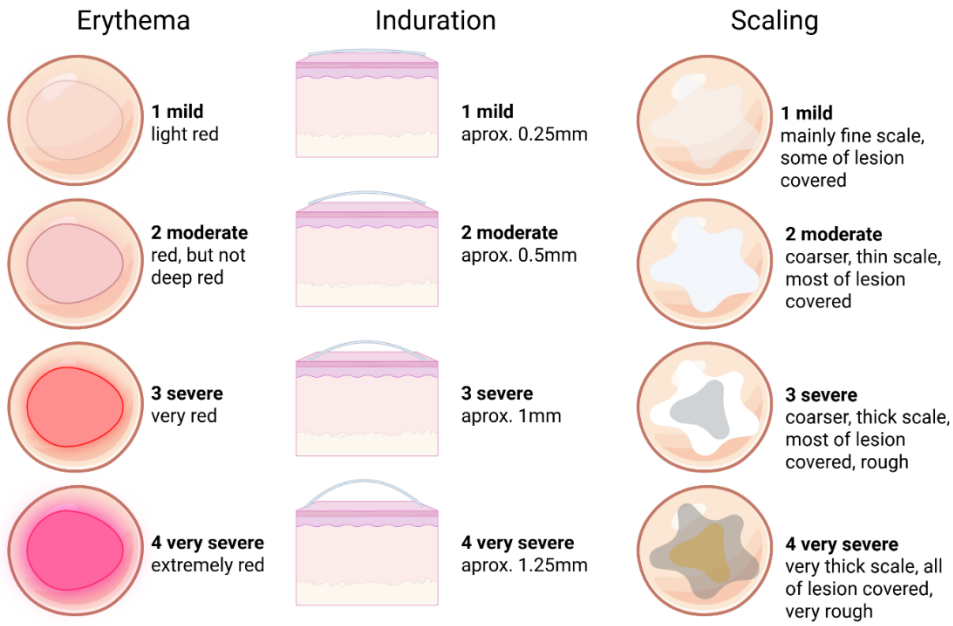


Figure 1: Psoriasis severity scoring guide by Psoriasis Area Severity Index. Created in BioRender. Pálsson, Ó. (2025) https://BioRender.com/dr8j3jv

The biomarkers of systemic inflammation should also be reported as they can be elevated during periods of high disease activity.[60] The erythrocyte sedimentation rate measured in mm/hour, and C-reactive protein (mg/L or mg/dL) are the most frequently reported markers of systemic inflammatory activity, and usually reported in trials.

Patient's assessment of quality of life, physical function, and disability is another core measure. It is a very broad category that includes physical and emotional well-being, work, social, leisure and family activity participation. Patients rate their physical function and the ability to perform daily activities as a top priority.[61] Measurement of these factors can be done in different ways, each with certain strengths and limitations.

The Health Assessment Questionnaire Disability Index (HAQ-DI) is commonly used and validated in RA and frequently collected in biologic DMARD databases for PsA. It assesses 8 categories: dressing, arising, eating, walking, hygiene, reach, grip and usual activity. It is a set of 20 questions, with at least two of each category. Each question has a four-level difficulty scale from no disability (zero), to complete disability (three). The highest component in each category determines the score for that

category.[62] HAQ-DI has been shown to be sensitive to changes in disability and is commonly reported in studies of PsA.[63]

The Short-Form 36 (SF-36) is a standardized patient-reported questionnaire used to assess functional health and well-being, it is normalized (mean = 50, SD = 10) with a score from 0-100, where higher scores indicate better health status.[64] It is derived from physical and mental component summaries (PCS/MCS) which are used in the calculation of a single composite score. EuroQol-5 (EQ-5D) is another generic measure of health-related quality of life. It assesses five domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. EQ-5D scores to a maximum of 1, which indicates full health, 0 indicates death and <0 indicates states worse than death. It has been validated for use in PsA.[65] It is collected in the Swedish Rheumatology Quality Register (SRQ), and reported in Study III.

One notable missing outcome measure from the OMERACT working group is the physician global assessment of disease activity, which is traditionally used in RA. This was considered to be captured in other indicators of musculoskeletal disease activity and may be subject to bias. It is also excluded from most of the composite scores. The physician global assessment of disease activity on a Likert scale of 0-4, where 0 indicates remission and 4 very high disease activity is collected in the SRQ.[66]

Composite scores of disease activity

A variety of composite scores exist to quantify disease activity, treatment response, and disease state. They differ between the domains included (skin, joints, enthesis, function) and each has strengths and limitations.Table 2 shows a summary of the different composite scores.

Disease Activity Index for Psoriatic Arthritis (DAPSA)

This score includes TJC, SJC, patient global assessment and pain VAS (0-10) as well as CRP measured in mg/dL. The formula is:

$$DAPSA = TJC68 + SJC66 + patient\ global + patient\ pain + CRP$$

The cut-offs for different disease states are defined as remission ≤ 4, low disease activity >4 to ≤14, moderate disease activity >14 to ≤28 and high disease activity >28.[67]

This score was developed from the OMERACT core domains, is sensitive to change and widely used in registry studies. It has variations to be applicable to different settings, such as clinical DAPSA (cDAPSA) which is calculated in the same fashion but excluding the CRP value.[68] Another

variation is DAPSA28 which uses the same formula but using 28 joint counts instead of 66/68 with a constant factor.[69]

$$DAPSA28 = 1.6 * TJC28 + 1.6 * SJC28 + patient\ global + patient\ pain + CRP$$

These scores focus rather heavily on joint outcomes, while important disease manifestations such as skin, nail, axial and entheseal disease are given less or no weight. DAPSA was initially designed in the year 2000 for assessment of reactive arthritis but in 2010 it was adapted to PsA.[70, 71] It has been validated for use in PsA with correctional, discriminatory and criterion validity. It has shown good correlation with ultrasound-assessed synovitis.[72]

The main limitation of using 28 joint counts is that it omits joints commonly affected in PsA, such as DIP joints and joints of the feet.[73] As the 66/68 joint counts are more widely used in the latter years, in registry studies extending back to the 1990s, 28 joint counts are often used as a substitute despite these limitations due to greater data availability. When performing registry studies, DAPSA28 should be preferred over Disease Activity Score of 28 joints with CRP (DAS28CRP) when only 28 joint counts are available.[74] This limitation is important in this thesis as it influences Studies III and IV.

DAS28CRP

Although it is not a composite measure of disease activity in PsA, this measure requires mention in this thesis as it is used in Study III. The calculation of DAS28CRP is as follows:

$$DAS28CRP = 0.56 * \sqrt{TJC} + 0.28\sqrt{SJC} + 0.014 * patient\ global + 0.36 * \ln(CRP + 1) + 0.96$$

It was developed for RA and is often considered the gold standard for assessing disease activity in RA. Disadvantages include the requirement of a blood test to calculate the score and the need for a computer or calculator to apply the formula.[75, 76]

Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA)

These criteria are widely used today. They are based on seven criteria and scores based on how many of them are fulfilled:[77]

1. TJC ≤ 1
2. SJC ≤ 1
3. PASI ≤ 1 or BSA ≤ 3%
4. Patient pain VAS ≤ 15mm (scale 0-100)
5. Patient global VAS ≤ 20mm (scale 0-100)
6. HAQ ≤ 0.5
7. Tender entheseal points ≤ 1

A patient fulfils the MDA if ≥5/7 criteria are met and VLDA if all 7 criteria are met.[78]

These criteria capture both joint and skin domains and has been shown to be specific for good disease control. MDA and VLDA are frequently used as treatment targets in trials.[79, 80] They are readily available in clinical settings and easy to calculate. They are simple for patients to understand when making shared treatment decisions.

Other

Bath Ankylosing Spondylitis Disease Activity Index and Functional Index are based on questionnaires which are answered on a VAS scale (BASDAI, BASFI, range 1-100) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are often applied when treating primarily axial PsA.[81-83] Bath Ankylosing Spondylitis Metrology Index (BASMI) records spinal mobility examination and is standardised for ankylosing spondylitis, and can be applied for axial PsA.[84]

Psoriatic Arthritis Disease Severity Score (PASDAS)

PASDAS is a weighted composite score of multiple domains including quality of life. It requires PCS scores from SF-36, is complex and is thus not practical in routine care or registries.[85]

Group for Research and Assessment in Psoriasis and Psoriatic Arthritis Composite Score – GRACE index

This score is a weighted composite score that includes five domains – joints, skin, pain, patient global and HAQ. It was developed to capture both articular and extra-articular disease. As with PASDAS, it is a complex calculation and not commonly used in clinical practice.[85]

Improvement criteria for clinical trials

Two criteria deserve mention here and apply to Study I. The most commonly used response criteria in clinical trials for new pharmaceuticals for PsA are the American College of Rheumatology response criteria (ACR).[86, 87] It is reported as the percentage of patients who improve ≥20% (ACR20), ≥50% (ACR50) and ≥70% (ACR70) in the core components SJC, TJC and three out of the following five measures: patient global VAS, physician global VAS, patient pain VAS, HAQ-DI, and acute phase reactant (either ESR or CRP).

The Psoriatic arthritis Response Criteria (PsARC) requires improvement in at least two of the following four measures, one must be a joint count, and no worsening in other components: TJC, SJC, patient global VAS and physician global VAS.[88, 89]

INSTRUMENT	DOMAINS COVERED	CRP OR ESR	REGISTRY FEASIBILITY	REMISSION CUT-OFF	NOTES
DAPSA/ DAPSA28	Joints, pain, patient global	Yes	Good	≤4	Simple, validated, no skin assessment
MDA/VLDA	Joints, skin, enthesitis, pain, HAQ	No	Moderate	5/7 or 7/7	Simple, multidomain
PASDAS	Joints, enthesitis, dactylitis, skin, PROs	Yes	Poor	≤1.9	Comprehensive but complex to calculate
GRACE	Joints, skin, pain, function	No	Poor	≤1.0	Research use
DAS28CRP	Joints, patient global	Yes	Good	≤2.6	Validated for RA, poor in PsA
BASDAI/BASFI ASDAS	Axial disease	±	Good	≤40* ASDAS≤1.3	Only for use in axial PsA

Table 2: Summary of the different composite criteria. *BASDAI/BASFI generally considered low when under 40 but no defined cut-off for remission.

Treatment

The treatment of PsA requires consideration of all disease domains, impacts on quality of life, and risk for irreversible structural damage.[8] Comorbidities and related conditions should be considered, and therapeutic decisions should be individualized to reflect patient preferences, made jointly by the patient and their physician. The treatment includes topical therapies for skin disease, physiotherapy, oral or intra-articular glucocorticoids as well as immunomodulatory medications. There have been great developments over the past three decades in the pharmacologic therapy of PsA, and where there earlier were few medical options, we now have a multitude of different therapies such as methotrexate, sulfasalazine, leflunomide and bDMARDs that target different parts of the inflammation cascade, such as inhibitors of TNF, IL-12/23, IL-17A/F and IL-23 as well as various targeted synthetic DMARDs such as Janus kinase (JAK) 1-3 inhibitors and the upcoming TYK-2 inhibitor to the JAK-STAT pathway.[8, 90] JAKs were initially named “just another kinase”, but later received their name from the two-faced Roman god of beginnings, endings and duality – Janus.[91] In addition, there are inhibitors to phosphodiesterase 4.[92] Multiple medications exist within some of the medication classes with an increasing number of biosimilars becoming available, making the armamentarium quite vast. Pharmaceutical therapy generally follows a treatment algorithm where methotrexate and/or TNF inhibitors are used as a first-line therapy. Figures 2 and 3 show the treatment algorithms according to the Group for Assessment and Treatment of Psoriasis and Psoriatic Arthritis (GRAPPA) from 2021 and the EULAR guidelines from 2024.[8, 9] ACR released another set of guidelines which was last published in 2018.[93] The Swedish Society for Rheumatology (Svensk Reumatologisk Förening) has similar guidelines for the management of PsA in Sweden.[94]

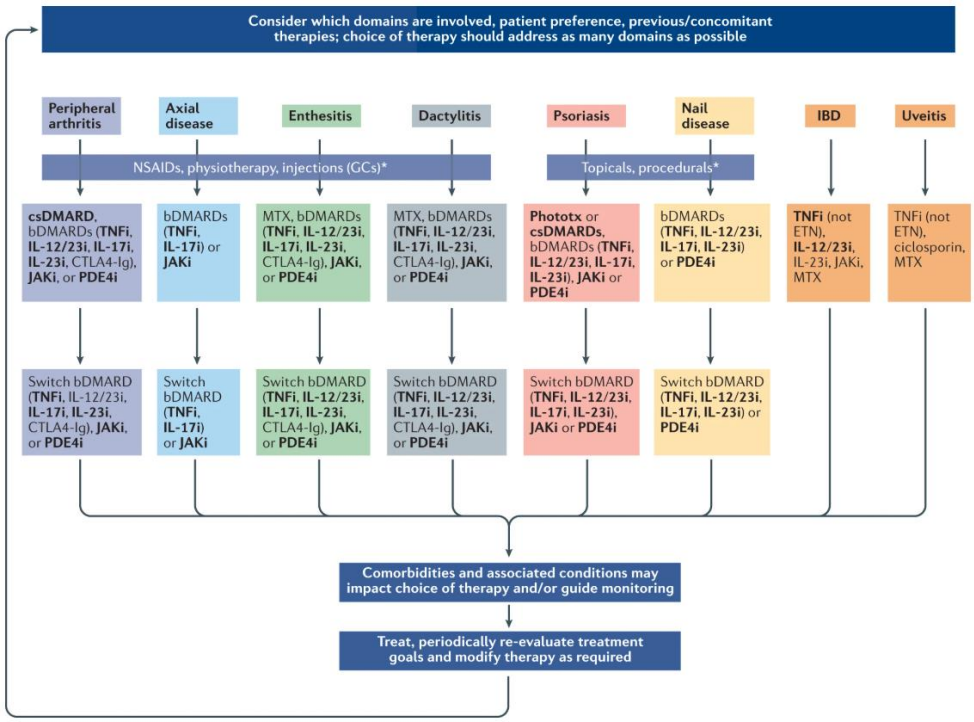
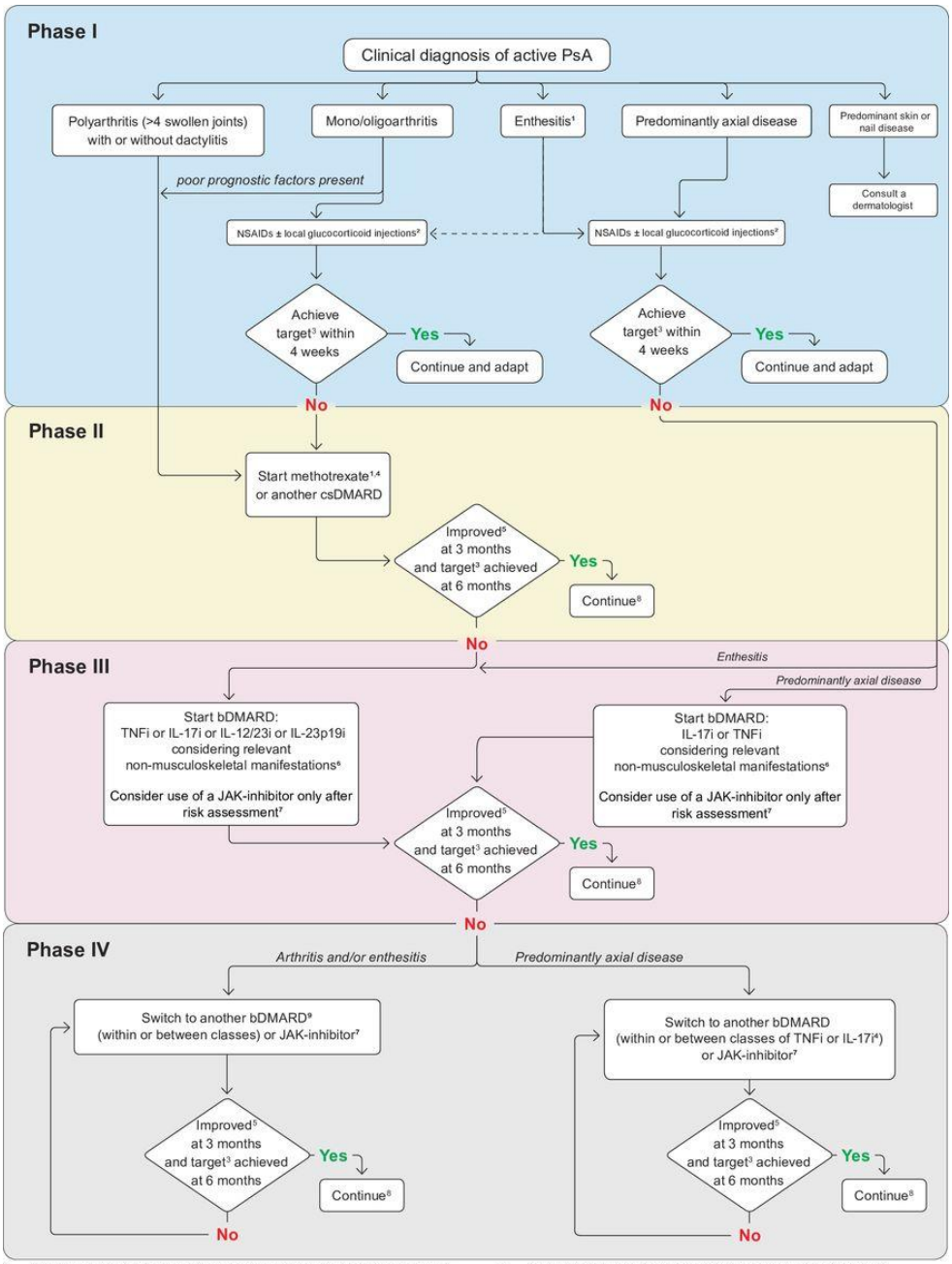


Figure 2: The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2021 treatment recommendations for psoriatic arthritis (PsA) use a domain-based approach, but, considering that most patients present with disease in multiple domains, this treatment schema combines the recommendations for each domain to guide therapeutic decisions. Disease activity should be assessed in each of the domains and consideration given to comorbidities, previous therapies and patient preference. Standard 'step-up' approaches, as well as expedited treatment routes, are indicated. Treatment efficacy and tolerability should be re-evaluated periodically and treatment adjusted as appropriate. The order of the products in the boxes is sorted by mechanism of action and does not reflect guidance on relative efficacy or suggested usage. Bold text indicates a strong recommendation, standard text a conditional recommendation. The asterisks indicate a conditional recommendation based on data from abstracts only. bDMARD, biologic DMARD; CTLA4-Ig, CTLA4–immunoglobulin fusion protein; csDMARD, conventional synthetic DMARD; ETN, etanercept; GC, glucocorticoid; IBD, inflammatory bowel disease; JAKi, Janus kinase inhibitor; MTX, methotrexate; PDE4i, phosphodiesterase 4 inhibitor; TNFi, TNF inhibitor. Reproduced from Coates, L.C., Soriano, E.R., Corp, N. et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol 18, 465–479 (2022). https://doi.org/10.1038/s41584-022-00798-0 Reproduced with permission from Springer Nature, no modifications were made.



1. *Some studies suggest that enthesitis may respond to methotrexate, but the level of evidence is low.*
2. *No glucocorticoids for axial disease.*
3. *The target is remission or low disease activity (especially with long standing disease) in accordance with the treat-to-target recommendations.*
4. *Preferred in the presence of relevant skin involvement, however in case of concomitant inflammatory bowel disease or uveitis, a TNF monoclonal antibody or (for IBD) IL-23i or 12/23i or JAKi is recommended.*
5. *Improvement means at least 50% reduction in disease activity.*
6. *Arthritis/enthesitis: TNFi or IL-17i or IL-12/23i or IL-23p19i; Skin: IL-17i or IL-12/23i or IL-23p19i; Uveitis: anti-TNF monoclonal antibody; IBD: anti-TNF monoclonal antibody or IL-12/23i or IL-23p19i or JAKi; Consider using PDE4i in mild disease if bDMARD and JAKi is inappropriate.*
7. *For JAK-inhibitors, caution is needed for patients aged 65 years or above, current or past long-time smokers, with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors or with other malignancy risk factors; with known risk factors for venous thromboembolism.*
8. *Consider tapering in sustained remission.*
9. *Including abatacept.*

Figure 3: 2023 EULAR recommendations algorithm for the management of PsA. bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; L, interleukin; JAK, Janus kinase inhibitor; JAKi, Janus kinase inhibitor; NSAID, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor; TNFI, tumour necrosis factor inhibitor. Reproduced from Gossec L, Kerschbaumer A, Ferreira RJO, et al EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update Annals of the Rheumatic Diseases 2024;**83**:706-719.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) remain a cornerstone in the symptomatic management of PsA and may be employed for joint pain in patients with psoriasis without overt arthritis.[8] They provide a rapid relief of pain and stiffness, by inhibiting the cyclooxygenase (COX) enzymes and thereby reducing prostaglandin synthesis. They are particularly useful in axial spondyloarthritis and are guideline recommended for axial PsA.[95] Despite their usefulness, NSAIDs do not modify disease progression and are primarily considered adjunctive therapy for symptomatic relief.[96] Salicin from willow trees has been known to have analgesic properties, but in 1897, Felix Hoffman, a German chemist, synthesised acetylsalicylic acid (aspirin) which was the first NSAID. Other NSAIDs were developed from the 1950s forward. Through the decades, the adverse effects of NSAIDs have become well documented, primarily gastrointestinal ulceration and bleeding, renal impairment and increased cardiovascular events.[97] The EULAR and GRAPPA guidelines both recommend NSAIDs as first-line for symptomatic relief or for mild disease provided there are no contraindications. The main contraindications are a previous diagnosis of ischemic cardiovascular disease, renal impairment or gastrointestinal ulcers. There are two general types of NSAIDs, non-selective COX inhibitors (such as ibuprofen, naproxen and diclofenac), and COX-2 selective inhibitors (such as etoricoxib and celecoxib) which may have fewer gastrointestinal side effects.[98]

Treat-to-target and tight control

Over the years, with the availability of multiple effective pharmacological treatments, the therapeutic landscape has changed drastically. In RA, the benefits of early intervention are well documented.[99] The physician should aim to see the patient early to initiate treatment as close to symptom onset as possible. Theoretically, interventions should be made in the early phases of the disease, where there is more acute inflammation and less chronic changes and damage.[100] Two treatment strategies are used to achieve this goal. *Tight control,* which involves assessing disease activity frequently in the early stages of disease to facilitate treatment escalations in a rapid and timely manner, and *treat-to-target* where a treatment target is agreed upon (e.g. achieving MDA, or remission according to DAPSA) and modifications or escalations to the treatment made until that goal has been achieved.[101-103] This has primarily been studied in RA, but in the landmark TICOPA (Effect of tight control of inflammation in early psoriatic arthritis) trial it was tested in PsA. It recruited adult patients with

early (<24 months symptom duration) PsA diagnosed by a consultant rheumatologist. It required no previous DMARD therapy and excluded pregnant and lactating women or who were planning a pregnancy. It randomised patients into "standard care" group which received therapy according to clinic guidelines, or "tight control" group where patients were seen by the study physician every four weeks and treatment was adjusted according to a predefined treatment protocol. The protocol introduced a new DMARD at regular intervals: methotrexate initially for 12 weeks, followed by sulfasalazine for 8 weeks, and allowing initiation of a TNF inhibitor at 20 weeks. At the end of the study, at 48 weeks, the "tight control" group achieved higher rates of ACR20/50/70 and PASI75 than the standard care group, although this was accompanied by a higher incidence of drug-related adverse events and increased cost of around £20,000-30,000 per quality-adjusted life-year.[79]

Sustained remission

Over recent decades, treatment goals have shifted from alleviating symptoms and preventing disability and radiological damage to achieving early and persistent or sustained remission. All of the outcome measurements and composite scores listed above, except the ACR and PsARC improvement criteria, measure the disease activity at a single point in time. While transient improvement and isolated visits in remission indicate effective short-term control, the concept of sustained remission reflects stable suppression of inflammatory activity over time. In RA, sustained remission has been linked with better long-term outcomes in physical function, quality of life and radiological progression.[104]

The concept of sustained remission has become accepted but there is no uniform definition of sustained remission. In the literature for RA, the definition of sustained remission varies and usually requires a state of remission in consecutive visits. The reported duration of sustained remission has been reported from several weeks to over a year.[105] In one study on RA conducted in Lund, Sweden, one visit with higher disease activity was allowed during the period of sustained remission without ending the remission period if the next visit was also in sustained remission. This approach is relevant in Studies III and IV.[106]

Studies III and IV primarily focus on the concept of sustained remission in PsA. Data on SR in PsA are limited, and lag significantly behind the RA literature. A retrospective study from Italy included 81 patients with PsA and defined sustained MDA if the criteria were met for at least 12 months of follow-up. They found a SR rate of 43% of patients treated with TNF

inhibitors.[107] A study from Canada defined remission as no actively inflamed joints at three consecutive visits over at least 12 months reported a 17.6% rate of remission in the pre-biologic era.[108] A recent Italian study investigating the efficacy of secukinumab in PsA, although not defining sustained remission, found drug retention rates of 66% after four years of therapy. 76.9% of biologic-naïve patients and 66.2% of non-naïve patients fulfilled MDA criteria.[109] Another Italian study including 80 PsA patients defined sustained remission as achieving ≤4 DAPSA and/or VLDA for at least 12 months. The sustained VLDA was achieved in 17.5% and sustained remission according to DAPSA in 30% in that study.[110] A study from Canada in 2020 using a very strict criteria of absence of swollen or tender joints and inflammatory back pain, VAS pain <15, VAS global <20, BSA <1%, HAQ <0.5 showed that remission occurred in 18% of patients and sustained remission (defined as remission at two consecutive visits) occurred in 9%.[111]

Gaps in knowledge and unmet needs

Limitations of Randomised Controlled Trials

Despite their central role in demonstrating efficacy, RCTs are conducted in highly selected populations, often excluding patients with comorbidities and fewer actively inflamed joints.[112, 113] Through evidence-based care we rely heavily on the results of RCTs to guide our treatment decisions. RCTs provide high-level evidence for efficacy of treatment, have high internal validity and can provide information on dose-response relationships. They are currently the industry gold standard for regulatory agencies prior to market approval for new medications. RCTs are regarded as the most rigorous proof of efficacy.[114] However, the strict inclusion and exclusion criteria often come at an expense of external validity, the results of such trials may not apply to large portions of the population, such as children, pregnant women, the elderly and patients with multimorbidity or polypharmacy.[115] For example, pivotal RCTs for TNF inhibitors excluded patients with significant cardiovascular disease and had restrictions on prior classical-synthetic DMARD (csDMARD) use.[89, 116-119] RCTs are complex to perform, patients are usually closely monitored and the adherance is tightly followed. They are expensive to conduct, and are often designed to demonstrate short- or medium-term efficacy. In inflammatory arthritis, there is often a significant focus on peripheral joint inflammation while many PsA patients have a predominantly entheseal or axial disease.[120]

Pain and analgesic use in inflammatory arthritis

Pain is a major contributor to disease burden in PsA, and despite optimal inflammation control and proportionally more patients in remission, a large proportion of patients still experience chronic pain.[121] Pain in inflammatory arthritis is a combination of peripheral inflammation, central pain sensitisation and psychological factors such as mood or prior emotional experiences.[121] While active synovitis contributes to nociceptive pain through inflammatory mediators, chronic pain may lead to nociplastic pain, termed widespread pain syndrome or fibromyalgia, which is a significant comorbidity in up to 20% of patients with inflammatory arthritis.[122]

Non-steroidal anti-inflammatory drugs (NSAIDs) remain a mainstay of treatment for stiffness and pain in PsA, and in milder disease they may even be used as monotherapy. However, long-term NSAID use is not without risks, including an increased risk of gastrointestinal bleeding, renal impairment and increased cardiovascular morbidity.[97, 123] Despite these risks, NSAIDs are extensively utilized, often in combination with csDMARDs or b/tsDMARDs to manage residual stiffness and pain. Understanding the use of NSAIDs in the biologic era is critical to evaluating treatment efficacy and safety.

Prevalence and predictors of sustained remission in PsA

PsA remains a chronic disease without a permanent cure. While achieving clinical remission is recognized as a key therapeutic goal in the management of PsA, it is equally important that the remission is maintained over longer periods of time. RCTs are generally conducted over a limited period of time, typically 1-2 years after the initiation of the study drug. The concept of sustained remission (SR) – remission maintained across multiple clinic visits, preferably over years, has been shown in RA to be associated with better long-term outcomes, including improved physical function, less pain and better quality of life.[124, 125] In PsA, however, the evidence of the benefits of SR remains scarce, as was outlined in the Sustained remission subchapter in the introduction.

Comparison of sustained remission rates between Sweden and Iceland

There may be substantial differences between different registries when investigating remission, and some registries may report different or even

contradictory predictive factors for remission.[126] Comparisons between registries may thus yield important insights to aid in identifying the optimal treatment strategies to achieve SR.

3 – AIMS OF THIS THESIS

The primary aim of this thesis is to examine the long-term treatment of psoriatic arthritis using real-world, prospectively collected data and to enhance the optimisation of biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) in psoriatic arthritis.

More specifically, the aims were:

I. To examine whether patients with PsA who would not have met the RCT inclusion criteria for TNFi therapy achieve comparable treatment outcomes (Study I).

II. To study the impact of TNFi initiation on NSAID use in patients with inflammatory arthritis, including PsA, compared to the general population (Study II).

III. To determine the prevalence and predictors of sustained remission in patients treated with b/tsDMARDs for PsA in Sweden (Study III).

IV. To compare the prevalence of sustained remission in patients treated with b/tsDMARDs for PsA in Iceland and Sweden, and explore potential differences (Study IV).

4 – STUDY POPULATION AND METHODS

This thesis is a compilation thesis including four registry-based observational cohort studies on patients with PsA. These studies were conducted using national clinical quality registries from Iceland and Sweden, with a longitudinal cohort design using prospectively collected data from routine clinical care.

Data sources

The Icelandic biologic registry (ICEBIO)

ICEBIO is the main database for patient registration and clinical follow-up for patients receiving b/tsDMARD therapy for inflammatory arthritis in Iceland.[127] It was launched in 2009 and is based on the Danish Registry for biological therapies in rheumatology (DANBIO) with adaptations to Icelandic conditions.[128] It is firmly incorporated into routine clinical care in Iceland, as data entry is required as a part of the prescription renewal process for b/tsDMARDs. It contains data on disease and treatment characteristics, markers of disease activity and physical function collected over time, for all patients receiving biologic therapy for rheumatic diseases. It currently holds information on over 98% of all patients receiving b/tsDMARDs for inflammatory arthritis in Iceland (personal communication).

At inclusion, the physician registers symptom duration and the date of diagnosis. Previous anti-rheumatic therapy can be documented into ICEBIO. At each visit the physician registers SJC, TJC, VAS global and enters CRP/ESR if available. Patient reported outcomes (VAS pain, fatigue, and global assessment of their health) as well as the HAQ questionnaire may be completed digitally at home prior to the visit, but these are usually collected at the clinic. The physician's and patient's data are used to calculate different composite scores such as DAS28CRP, DAPSA and HAQ.

Swedish Rheumatology Quality Register (SRQ)

The SRQ was established in 1996 and has since been prospectively collecting data on patients with rheumatic disease.[129] It is an extensive registry which covers over 100 rheumatic diagnoses and includes over 89,000 patients. Physicians, nurses, physiotherapists and occupational

therapists from 56 rheumatology units across Sweden can enter health data into the registry. In addition, it includes a module where patients enter information about their well-being prior to every physician visit. This registry has excellent coverage with longitudinal information on over 14,000 patients with PsA and an estimated coverage of over 90% of patients with PsA receiving b/tsDMARDs in Sweden.[130] The use of the registry is a part of routine clinical care, and both patients and physicians are encouraged to make regular registrations at each patient visit.

At inclusion into the SRQ, baseline data on symptom onset, date of diagnosis and previous anti-rheumatic therapy are collected. At each follow-up visit the physician records SJC, TJC, physician global VAS and CRP/ESR. Changes to the anti-rheumatic treatment are collected. Patient reported outcomes are done either at home or at the rheumatology clinic digitally. The physician's and patient's data are used to calculate different composite scores such as DAS28, DAS28CRP, DAPSA, HAQ and EQ-5D.

Prescription Medicines Register (in Iceland)

For Study II, ICEBIO was linked to the Icelandic Prescription Medicines Register (Lyfjagagnagrunnur Landlæknis). It was established in 2005 and has a coverage of over 90% of all prescriptions in Iceland. Since 2013, following legislative change, the register achieved near-complete coverage of all prescriptions made in Iceland. It records not only prescriptions but also dispensations from pharmacies in real-time. Drug prescriptions are covered by a national health insurance, increasing stepwise to 100% of drug costs at around €3500 per year, encouraging prescriptions even for medications that are available over the counter.

Registers Iceland

For Study I, we acquired age- and sex-matched comparators from the official civil registry of Iceland, Þjóðskrá (e. Registers Iceland).[131]

Study population and methods

Study I – RCT eligibility

All patients with PsA registered in ICEBIO who initiated their first TNF inhibitor (adalimumab, etanercept, infliximab or golimumab) between January 2000 and February 2016 were included. Certolizumab pegol was not available in Iceland during the study period and is therefore not included. Patients were previously classified by *Runarsdottir et al* based on whether they would have met the inclusion criteria for the RCTs that

supported the market approval of their respective TNF inhibitor (Figure 4).[113, 116-119, 132] Each patient had been classified according to the trial-specific criteria from published protocols. The inclusion criteria varied across trials, but common inclusion criteria were patients who fulfilled the CASPAR criteria, having ≥3-6 swollen and ≥3 tender joints with inadequate response or intolerance to ≥1 DMARD. Common exclusion criteria were significant comorbidities such as evidence of tuberculosis or clinically significant cardiovascular disease, for example, in the IMPACT 2 study of infliximab, patients with New York Heart Association class III-IV heart failure, unstable angina or recent myocardial infarction were excluded.[117] Some restrictions were made on prior DMARD therapy or recent use of high-dose glucocorticoids.

Approvals for b/tsDMARD therapy in Iceland are granted by the Medicines Committee at Landspítali University Hospital through an application process. The first approval for a b/tsDMARD treatment is usually valid for six months and subsequent approvals for continued therapy are valid for one year at a time. Thus, visits in ICEBIO are often registered around the six- and 18-month marks after initiation. Visit data are acquired at the baseline visit, then at six (nearest visit to 180 days (range 90-210)) and 18 months (nearest visit to 540 days (range 211-570)).

Out of 329 patients with PsA registered in ICEBIO as of 2016, 274 initiated their first treatment with a TNF inhibitor, and 226 could be classified based on the data available from previously published studies. In total, 74 patients (33%) would have fulfilled the inclusion criteria, and 152 patients (67%) would not have fulfilled the inclusion criteria. The most common reason for exclusion was an insufficient number of swollen joints (45%), followed by comorbidities (16%).[113]

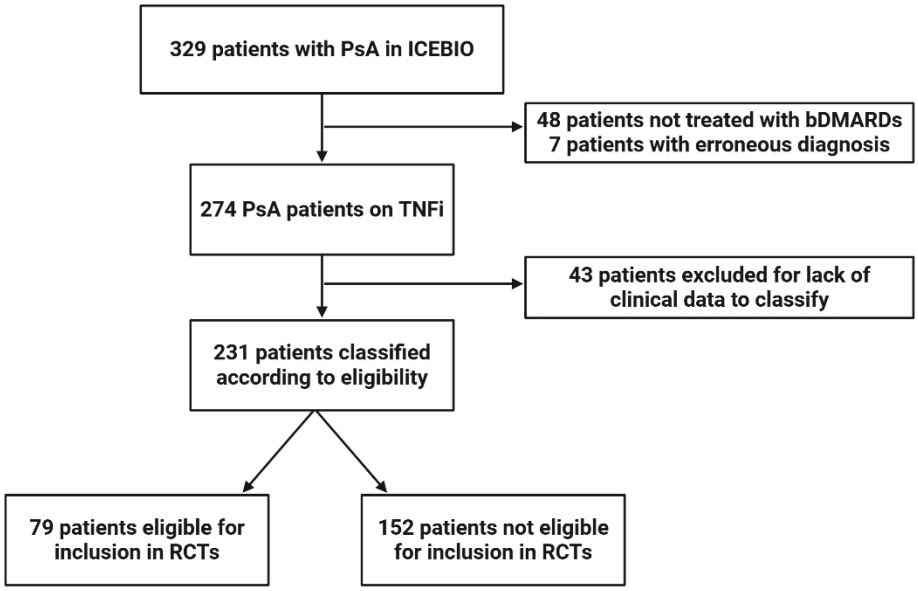


Figure 4: Study population for Study I. Created in BioRender. Pálsson, Ó. (2025) https://BioRender.com/qkpstlv

Study II – NSAID use

All patients with PsA, RA and axial spondyloarthritis registered in ICEBIO and initiating a first TNFi course in 2005-2015 were included. We extracted patient characteristics, disease activity and functional data for each patient from ICEBIO as well as the TNFi initiation date. Five age- and sex-matched comparators for each patient were extracted from Registers Iceland (Figure 5). All dispensed electronic prescriptions for non-opioid analgesic medications (ATC codes M01A, M01B and N02B) during a timeframe of 2 years before and after the TNFi initiation date were retrieved from the IPMR for all patients, and their respective matched comparators. Since only dispensed medications are retrieved, we assume that each dispensed analgesic was consumed and converted the prescriptions to Defined Daily Doses (DDD) as defined by the World Health Organization (the assumed average maintenance dose per day for a drug used for its main indication in adults).[133]

Patients were divided into subgroups based on their diagnoses registered in ICEBIO. NSAID consumption was then estimated before and after initiation of TNFi therapy. Physician and patient reported outcomes were

compared for the quintile with the highest DDDs of NSAIDs compared to the lower four quintiles.

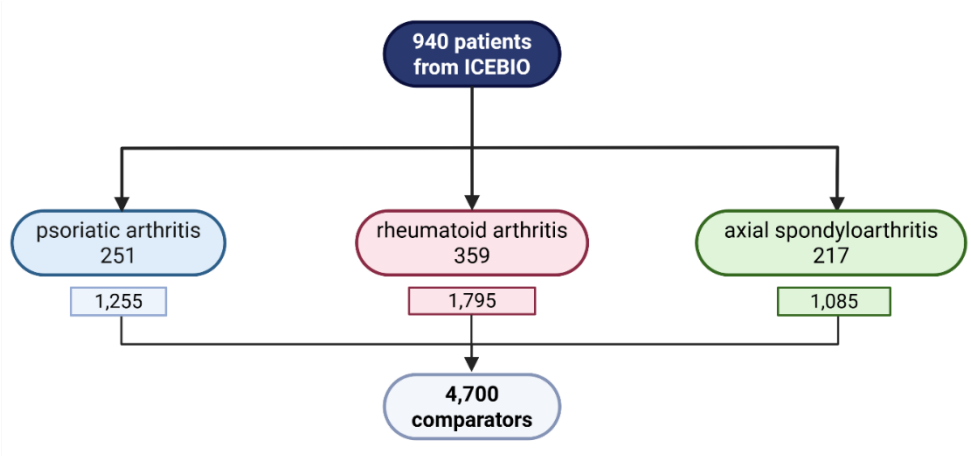


Figure 5: Study population for Study II. Created in BioRender. Pálsson, Ó. (2025) https://BioRender.com/04wyi9s

Study III – Sustained Remission

All patients registered in the SRQ and treated with b/tsDMARDs for PsA between April 1999 and December 31, 2017 were extracted from the registry in 2019 to ensure at least two years of follow-up data as per the study assessment period. The baseline visit was defined as the first registered visit with b/tsDMARD therapy. Sustained remission was defined as meeting the criteria for remission at ≥2 visits for ≥6 months. At least two years of follow-up were required, and to be eligible for assessment of SR, a minimum of three visits during that period was required (Figure 6). Patients were followed from the baseline date of initiation of a first b/tsDMARD onward, thus the first SR did not necessarily occur during the individual's first b/tsDMARD treatment course.

The primary outcome of this study was the proportion of patients who reached remission or SR at any point during the follow-up. Remission and SR were assessed using three different disease activity scores, DAPSA28, DAS28CRP and physician global assessment on a Likert scale of 0-4. Other measures of disease activity were explored but not available for assessment due to high levels of missing data. Additionally, we performed the same analysis but with SR instead defined as lasting ≥12 months.

One visit with higher disease activity was allowed during a period of SR without ending the SR period to account for factors that may temporarily

increase disease activity indicators but are not due to worsening disease (for example, joint pain and elevated CRP during a viral infection). This visit was omitted from the SR period as long as (1) the b/tsDMARD therapy was not altered and (2) the prior and subsequent visits were less than two years apart. Similarly, we allowed for one visit with missing data without ending the period of SR using the same criteria. Each SR period could only have one visit omitted in this fashion. We performed a sensitivity analysis with a more stringent definition where this omitted visit was not allowed. As secondary outcomes, possible baseline predictors of ever reaching SR were explored by investigating all available potential predictors.

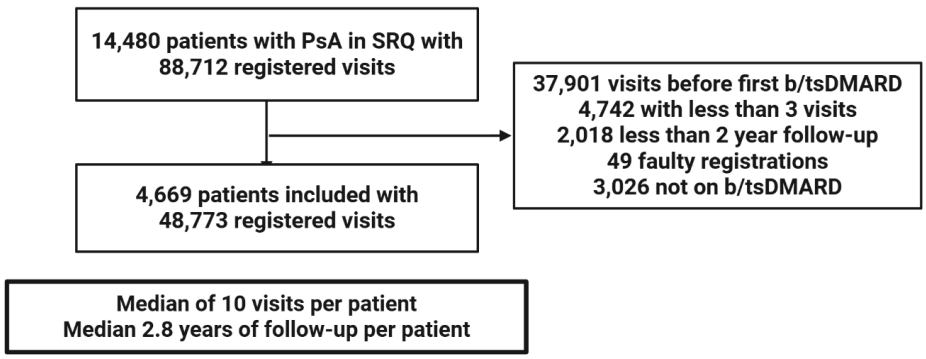


Figure 6: Study population for Study III. Created in BioRender. Pálsson, Ó. (2025) https://BioRender.com/nx366w2

Study IV – Comparison between remission rates in Iceland and Sweden

All patients registered in the SRQ and treated with a b/tsDMARD for PsA between April 1999 and June 2023 were retrieved. Similarly to Study III a minimum of three visits and two years of follow up is required, and thus all visit data were extracted until June 2025 (Figure 7). Sustained remission was assessed using the same definition as in Study III, but only for DAPSA28. Similarly, one flare or visit with missing data was allowed and we performed a sensitivity analysis where this flare was not permitted.

The main outcome was to compare SR rates between Iceland and Sweden and to explore predictive factors in Iceland. The second main outcome was to explore time trends in sustained remission frequency in Iceland.

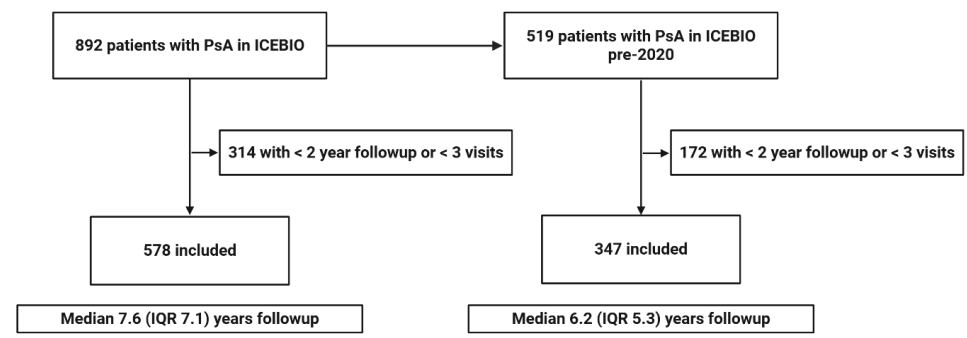


Figure 7: Study population for Study IV. Created in BioRender. Pálsson, Ó. (2025) https://BioRender.com/hjib88m

Ethics

All studies in this thesis were observational and non-interventional, based on routinely collected data from registries and databases. Study I and II protocols were approved by the National Bioethics Committee and the Icelandic Data Protection Authority (Study I: VSNb2015120017/03.03, Study II VSNb2018010003/03.01). Study III and IV were approved by the Regional Ethics Review Board in Lund, Sweden, (Dnr 2014/754), and requirement for the individual patient consent was waived as per the ethical approval. Study IV was approved by the National Bioethics Committee (VSNb2022030026/03.01).

Statistical analyses

All data preprocessing and statistical analysis were performed in Microsoft Excel and R (R Project for Statistical Computing, Vienna, Austria) for all four studies. In addition, Python (version 3.13.2) was used for Study IV to calculate periods of sustained remission. Descriptive statistical methods were used to describe baseline demographics and clinical characteristics.

In most registry studies, there are significant proportions of missing data. This is inherent to registries and has multiple causes, including incomplete data entries, irregularities in the timing of follow-up visits, variations in clinical routines or withdrawal from the registry due to factors such as patient moving out of the clinic's uptake area. In rheumatology registers, patient reported outcomes are often missing, especially before the electronic collection of data. There are also shifts in the management

guidelines over long periods of time, such as the collection of only 28 joint counts in the earlier years of the registries, leading to a lack of reliable 66/68 joint counts. The pattern of missing data is rarely completely at random; it is expected to relate to disease activity, treatment response, or clinic workload. Whether data are missing completely at random (MCAR) or missing not at random (MNAR) affects the appropriate statistical strategy to employ. Common statistical approaches include complete case analysis or methods of multiple imputation.

Study I

Unpaired t-tests were performed on improvement scores between the included and excluded groups. To account for missing data in the response criteria, we employed the LUND Efficacy indeX (LUNDEX) method (Fraction of starters still in the study at time T) x (Fraction responding at time T).[134] Drug survival was illustrated using a Kaplan-Meier curve, with a log-rank test between the included and excluded group curves.

Study II

Because of a logarithmic distribution of prescriptions, non-parametric bootstrapping was performed to calculate the yearly doses consumed of NSAIDs. Bootstrapping is a method to estimate the precision of an estimate in a skewed or unknown distribution of data. In simplified terms, one has a dataset which is a subset of the population from which one gets a single mean with no distribution data. With bootstrapping one takes a sample of data from the dataset to get another mean, replaces the data and samples again, often 1,000-50,000 times. Thus, the mean acquires accuracy and confidence intervals. The method increases the robustness of the statistics but uses much computational power. The term bootstrap derives from the phrase “to pull oneself up by one’s bootstraps”, which is thought to be based on the *Adventures of Baron Munchausen* by Rudolph Erich Raspe. The Baron had fallen to the bottom of a lake, and all seemed lost until he thought to pick himself up by his own bootstraps.[135]

Unpaired t-tests were performed when comparing doses between patients and comparators, when comparing disease outcome measures between the highest quintile consumers and the other four quintiles as well as when comparing prescription amounts before and after TNFi initiation.

Study III

A multiple imputation procedure based on a Random Forest algorithm was used to impute missing values among the baseline covariates. The dataset

was randomly divided into two parts, 75% for training purposes and 25% for testing. Possible predictors from available data were selected using the Boruta algorithm.[136] Several predictive models were explored to model the likelihood of reaching SR: logistic regression, elastic net, extreme gradient boosting, and k-nearest neighbors. Logistic regression exhibited comparable accuracy to the other models and was chosen for this study, with the added benefit of interpretability. We performed univariate and multivariate logistic regression models incorporating possible predictors selected by the Boruta algorithm.

Study IV

A multiple imputation procedure based on a Random Forest algorithm was used to impute missing values among the baseline covariates. Univariate and multivariate logistic regression models were employed to identify predictors for sustained remission. This results in methodologically similar findings that are comparable to Study III.

5 – RESULTS

Eligibility of RCT inclusion (Study I)

The included and excluded groups in the previous study by *Runarsdottir et al* were broadly similar in demographics.[113] The mean age was approximately 50 years and 55% were female. Mean disease duration was around 7 years, and the average BMI was around 30 kg/m^2, consistent with mild obesity in the cohort, as expected in patients with PsA. As with all registry-based studies there are significant missing data, especially at six and 18 months, even though the time range in which these visits occurred was cast wide.

The disease activity markers were similar between the groups except that the included group had a higher mean SJC and subsequently a higher DAS28CRP. At 18 months the excluded group had a slightly higher CRP.

Response to therapy

There were no significant differences between groups in ACR20, DAS28CRP or DAPSA28 responses, although fewer in the excluded group reached ACR50. When correcting for lost to follow-up or missing data using the LUNDEX method, there was no statistically significant difference at six and 18 months in any of the composite scores except ACR50.

Improvement in clinical scores (n)	6 months		18 months	
	Included	Excluded	Included	Excluded
ACR response available	26	52	26	49
ACR20	77%	60%	69%	59%
ACR50	58%	40%	65%*	37%*
ACR70	27%	23%	50%	28%
DAS28CRP available	26	51	26	51
DAS28CRP response	77%	71%	81%	67%
DAPSA28 available	23	46	24	49
DAPSA28 response	83%	70%	75%	71%

Table 3:. Response to first TNF inhibitors, percentage achieving response by ACR criteria or decrease in disease activity by DAS28CRP or DAPSA28. * Denotes a p value of <0,05 by unpaired t-test on testing for the statistical difference between included and excluded groups (both columns designated *) *ACR20/50/70 American College of Rheumatology response criteria, improvement by 20%/50%/70%; DAPSA28 Disease Activity Score in Psoriatic Arthritis for 28 joints; DAS28CRP Disease Activity Score 28-joint count C reactive protein.* Reprinted with permission from BMJ Publishing Group Ltd.

Drug retention

The two groups had similar 2-year drug survival, with 46% of patients having discontinued therapy at the end of the second year in the included group and 44% in the excluded group (Figure 8). No statistically significant difference was found between the curves.

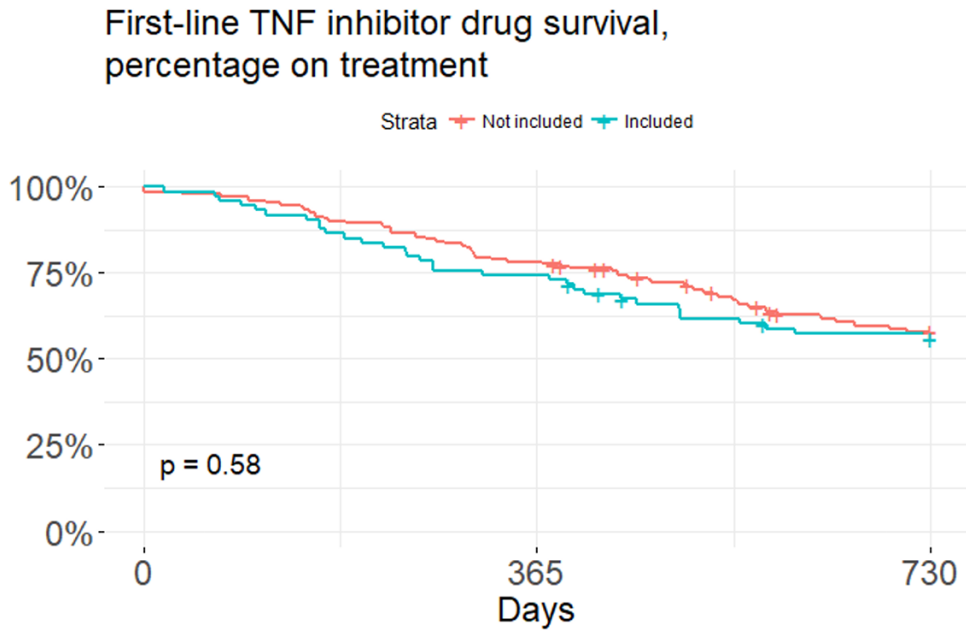


Figure 8: Drug survival curves of all patients with psoriatic arthritis receiving their first biological disease-modifying antirheumatic drug, divided by their eligibility for clinical trials. Included group in blue, excluded group in red. Log-rank test between the curves showed no statistical difference, p=0.58. Reprinted with permission from BMJ Publishing Group Ltd.

In a previous Icelandic study, it was shown that two-thirds of patients with PsA starting TNFi in routine care would not have met the eligibility criteria for the RCTs that led to their respective drug market approval.[113] Yet, we demonstrate that their treatment response and drug survival were comparable to the trial-eligible patients. Thus, treatment outcomes for bDMARD treatment in PsA from RCTs may likely be applied to daily clinical practice, irrespective of whether patients would have fulfilled their inclusion criteria or not.

NSAID consumption (Study II)

The PsA group patients had a mean age of 49 with 59% being female. The mean disease duration was 7.4 years and BMI was 30.4. This was comparable to the other groups studied except for BMI which was slightly higher, as expected in PsA. The most used TNF inhibitor was infliximab, consistent with the Icelandic treatment guidelines during the study period.

The cut-off points between the highest fourth and fifth quintiles in NSAID use were 225 DDD/year for PsA, 213 DDD/year for RA and 199 DDD/year for axial spondyloarthritis.

	Patients 2 years before the start of TNFi treatment	Comparators corresponding 2 years period before baseline	Patients 2 years after the start of TNFi treatment	Comparators corresponding 2 years period after baseline
All patients	150 (154, 160)	22 (23, 24)	85 (89, 93)	22 (23, 24)
Rheumatoid arthritis	148 (155, 166)	29 (30, 33)	86 (91, 99)	28 (29, 32)
Psoriatic arthritis	157 (165, 178)	19 (20, 22)	90 (97, 108)	20 (21, 24)
Ankylosing spondylitis	153 (160, 172)	16 (17, 19)	80 (86, 95)	15 (16, 18)
Other arthritis	132 (142, 157)	21 (23, 28)	83 (92, 106)	23 (25, 29)

Table 4: Data are presented as bootstrapped mean (75^{th}, 95^{th} percentile) defined daily doses (DDD)/patient/year. Comparing patients to comparators with an unpaired t-test shows $p<0.0001$ for all groups both before and after TNF inhibitor initiation, as well as when comparing patients before and after TNF inhibitor initiation. No difference was found between comparators before and after baseline. Reprinted with permission from Taylor & Francis.

Patients with PsA averaged 157 DDD NSAIDs/patient/year and decreased to 90. Thus they consume around 8 times more NSAIDs than their age- and sex-matched comparators. The consumption decreases to 90 DDD NSAIDs/patient/year in the two years following the initiation of a TNF inhibitor, which is a reduction of 43%. These numbers are similar to patients with RA or axial spondyloarthritis who also gain a similar benefit in the reduction of NSAID consumption (Table 4, Figure 9).

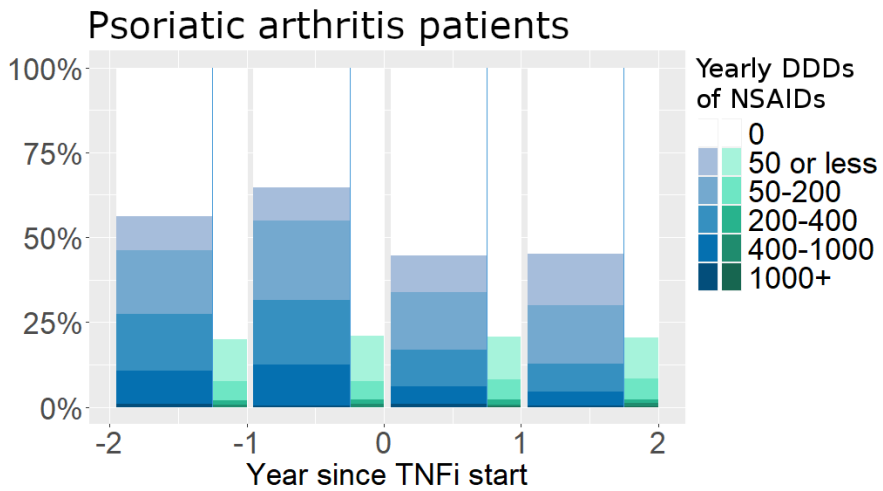


Figure 9: Dispensed non-steroidal anti-inflammatory drug (NSAID) prescriptions 2 years before and 2 years after TNF inhibitor initiation in patients with PsA. Each column represents the cumulative defined daily dose (DDD) of NSAIDs per year in patients (wider blue columns) and comparators (narrower green columns). Reprinted with permission from Taylor & Francis.

When comparing the highest quintile of NSAID consumers to the other four quintiles in PsA, no differences were found in any patient or physician reported outcomes (SJC28, TJC28, physician global VAS, CRP, patient pain, fatigue and global VAS or HAQ). The highest amount of missing data in the physician and patient reported outcomes was 31%. No imputation was performed in this subanalysis.

Sustained remission (Studies III+IV)

Prevalence

In the Swedish data from Study III, 54% never achieved a state of remission and 24% of patients achieved a period of sustained remission for six months according to DAPSA28. According to DAS28CRP, 19% of patients never achieved remission and 54% achieved SR. According to the physician global on a Likert scale, 31% of patients never achieved remission and 38% achieved SR. When extending the definition of sustained remission up to 12 months, the corresponding numbers are 22% for DAPSA28, 53% for DAS28CRP and 36% for physician global on a Likert scale (Figure 10).

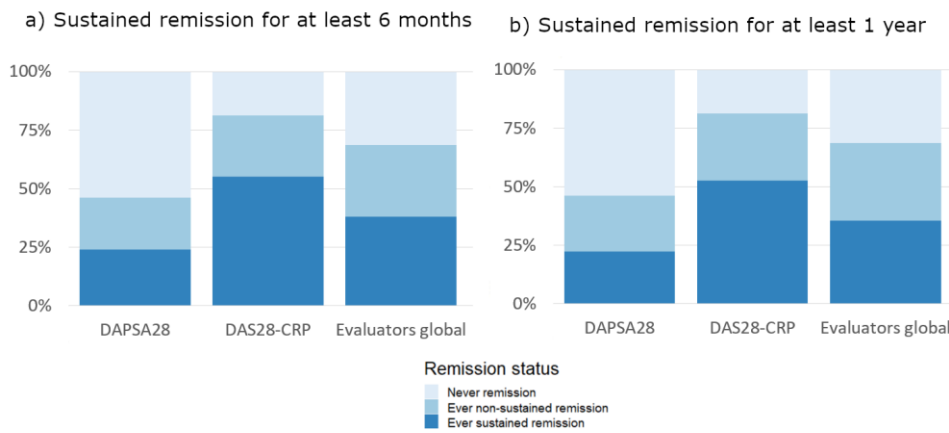


Figure 10: Proportion of patients achieving sustained and non-sustained remission at any point after the initiation of b/tsDMARD therapy, until the end of follow-up for a) six months and b) one year. Reprinted with permission from Journal of Rheumatology Publishing co. Ltd.

In the Icelandic data from Study IV, 48% had never experienced remission and 33% attained SR for at least six months.

Predictive factors

Out of the factors explored at the baseline visit, younger age, male sex, non-smoking status, lower SJC28, lower CRP and lower ESR, lower patient fatigue, pain and global VAS, lower HAQ, better EQ-5D utility, treatment with NSAIDs or any csDMARDs and earlier year of inclusion in the study were all univariately associated with a higher likelihood of achieving SR (with the six-month definition, all three composite outcome scores). After adjustment in the multivariate analysis, only fewer swollen joints at baseline remained a significant predictor of ever reaching SR according to all three disease activity measures (Figure 11).

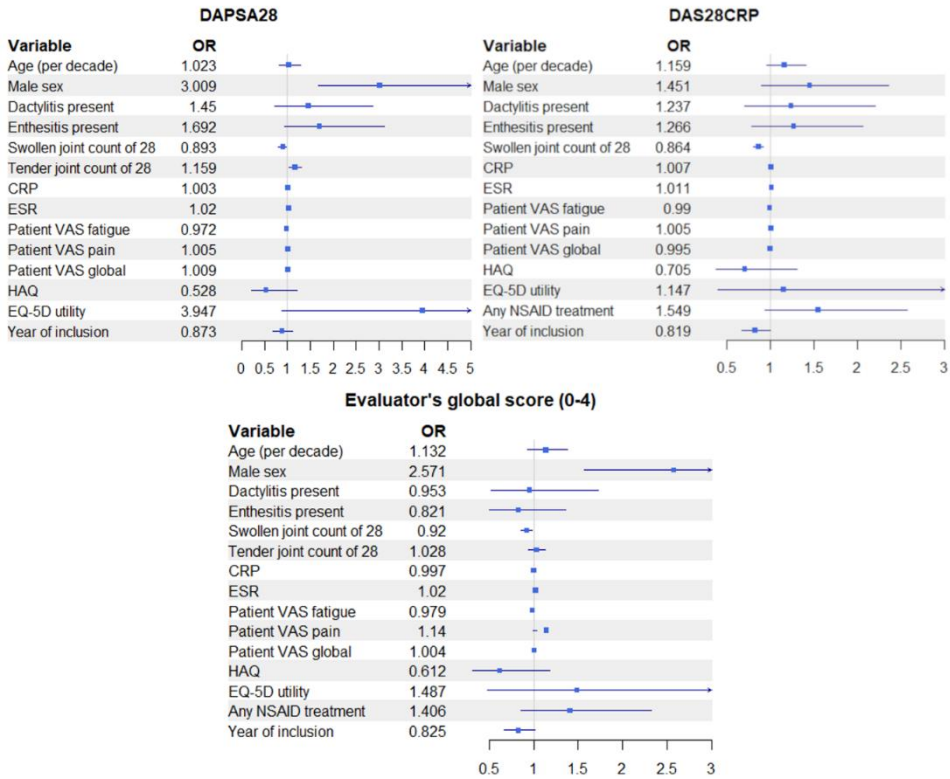


Figure 11: Predictors at the start of a first b/tsDMARD of ever achieving SR in multivariate logistic regression analyses. Reprinted with permission from Journal of Rheumatology Publishing co. Ltd.

Comparison between two Nordic countries

When comparing the pre-2020 Icelandic data to Sweden, 53% of patients with PsA never achieved remission at any time point, which is similar to 54% in Sweden from Study III. In total, 29% ever achieved SR which is slightly higher than the Swedish population where 24% achieved SR. When extending the definition of SR to last at least 12 months the numbers were 25% and 22%, respectively (Figure 12). In Iceland, male sex, lower TJC28, high CRP, lower fatigue and higher physician global VAS as well as a lower HAQ were associated with SR for ≥6 months. In the Swedish dataset, we identified male sex, lower SJC28, higher TJC28 and lower patient VAS fatigue as predictive factors for SR. Both studies thus identify male sex and VAS fatigue as predictive factors for SR. Male sex and lower patient VAS fatigue were common to both studies, but they differed in SJC28, physician global VAS and CRP and diverged in TJC28 (Table 5).

In Iceland, the first SR period lasted for a median (median (IQR, range) 3.3 (3.1, 0.6-17.6) years. Infliximab was the active treatment during the SR period in 40%, etanercept in 26% and adalimumab in 24%.

	ICEBIO study	SRQ study
Male sex	1.79 (1.19-2.70)*	3.01 (1.68-5.52)*
TJC28	0.92 (0.85-1.00)*	1.16 (1.04-1.31)*
C-reactive protein (mg/L)	1.03 (1.01-1.05)*	1.00 (0.98-1.03)
Patient VAS fatigue	0.84 (0.74-0.96)*	0.97 (0.96-0.99)*
Physician VAS global	0.98 (0.84-1.14)*	1.00 (0.99-1.03)
HAQ	0.59 (0.38-0.91)*	0.53 (0.22-1.21)
SJC28	0.95 (0.87-1.05)	0.89 (0.80-0.98)*

Table 3: Comparison of significant predictors at the start of the first b/tsDMARD of ever achieving SR for ≥6 months in multivariate logistic regression analyses, comparison between results from this study and the prior study by *Palsson et al*.[137] * Denotes a p value of <0,05 in the respective study.

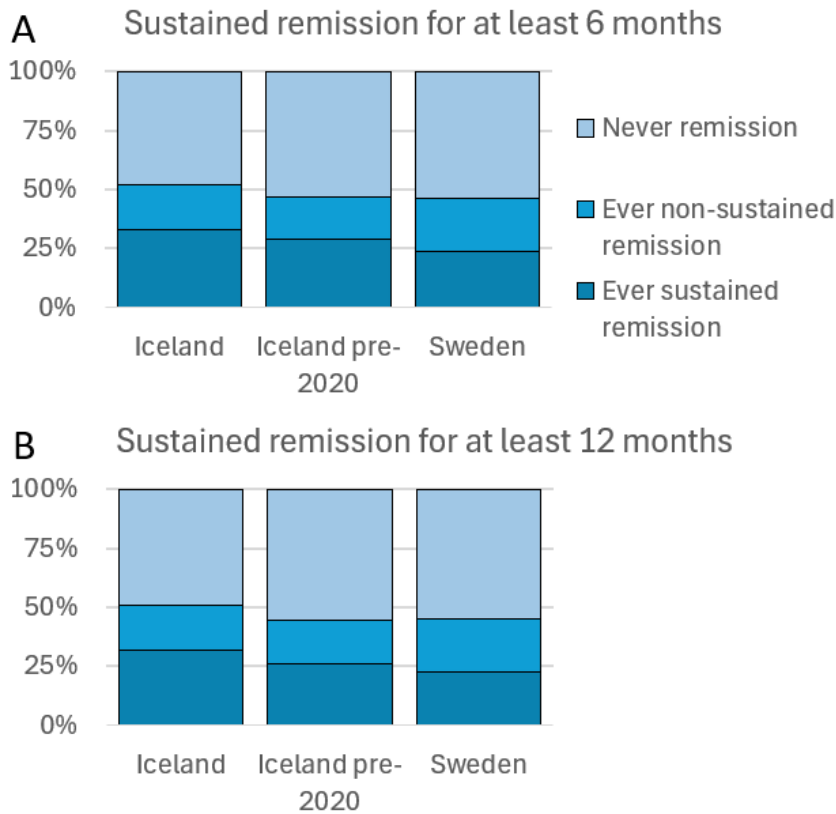


Figure 12: The proportion of patients achieving sustained and non-sustained remission as defined by Disease Activity in Psoriatic Arthritis with 28 joint counts at any point after the initiation of the first b/tsDMARD therapy until the end of follow-up. (A) SR lasting for ≥6 months (B) SR lasting for ≥12 months.

6 – DISCUSSION

Generalisability of randomised trials

RCTs are the foundation of evidence-based practice in medicine. Their strength lies in a rigorous design, randomisation and blinding to minimise bias and maximise internal validity, and in the ability to attribute observed outcomes to the intervention performed. However, these same strengths may come at a cost of reduced external validity, potentially limiting the generalisability and applicability of the trial results to the more diverse patient populations we encounter in daily clinical practice.

RCTs of TNF inhibitors in PsA typically include a selected patient group with more active disease. They require fulfilment of a classification criterion such as CASPAR, selects for severe peripheral arthritis, commonly requiring at least six swollen joints. There are limitations on comorbidity and stable use of other medications preceding inclusion into the trial, such as csDMARDs and corticosteroids. Such stringent entry criteria are necessary to demonstrate treatment efficacy with sufficient statistical power (increasing internal validity) but exclude the even larger group of patients with milder disease or common comorbidities. Consequently, two-thirds of Icelandic PsA patients would not have fulfilled the inclusion criteria for the RCTs.

In our nationwide Icelandic study (Study I), we evaluated treatment effectiveness and drug survival of first-line TNF inhibitors in patients with PsA who would not have been included in the RCT leading up to the market approval of their respective drug. Despite not fulfilling these criteria, treatment response and drug survival were comparable between those eligible and ineligible for RCTs, at six and 18 month follow-up visits. These findings suggest that the benefits of the medications observed in RCTs likely extend to a broader spectrum of patients. This is in line with previous research in RA, which showed that patients ineligible for RCTs still responded to TNF inhibitors, but had lower treatment response.[138] Another study found that only a minority of patients with RA would have been eligible, but the most common reason for exclusion would be low disease activity, specifically low joint counts, which is similar to our study.[139]

National registries such as ICEBIO and SRQ provide real-world, prospectively collected data and play a pivotal role in translating the efficacy of RCTs to effectiveness in everyday clinical practice. By capturing longitudinal data on treatment response, safety and persistence

across the whole patient spectrum, they provide the evidence needed to bridge the gap between RCTs and clinical reality. Such data can inform guideline development and support healthcare policy decisions on the use of novel medications which are sometimes of high financial cost. RCTs remain indispensable for establishing safety and efficacy, while registries allow for a more complete understanding of drug effectiveness and safety, specifically in the long term.

Indirect benefits of optimal medical therapy

The primary goal of treating patients with psoriatic arthritis is to maximise health-related quality of life, through control of symptoms, prevention of structural damage, normalisation of function and social participation; abrogation of inflammation is an important component to achieve these goals.

EULAR treatment guidelines for psoriatic arthritis
overarching principle D

The primary goal of medical therapy in PsA is to reduce inflammation, prevent joint damage and preserve function. Even though the abrogation of inflammation is important, maximising health-related quality of life and normalisation of function and social participation are not always achieved through the use of immunosuppressive drugs. Function, pain and fatigue are sometimes severely affected in the absence of demonstrable inflammation, and there is concomitant fibromyalgia in 18% of patients which has many overlapping symptoms with PsA.[122]

The first-line medical treatment for pain and stiffness remains NSAIDs, both pre- and post-bDMARD therapy, due to their rapid onset and good efficacy. In our Icelandic nationwide study (Study II), initiation of TNF inhibitor therapy was followed by a marked reduction in the use of NSAIDs in PsA as well as other arthritides. NSAID consumption declined by 43% in the years following TNF inhibition and the proportion of patients receiving NSAID prescriptions decreased significantly. This reduction indicates not only symptomatic improvement but also that optimal disease control alleviates the need for analgesic therapy. NSAID use either intermittently or chronically is associated with gastrointestinal bleeding, renal morbidity and increased cardiovascular risk.[97, 123] The decline in the use of NSAIDs represents an indirect safety benefit of adding bDMARD therapy, which is especially important in PsA patients where comorbidities such as obesity and metabolic syndrome are common and contribute to an increased risk of cardiovascular complications.

Despite improved medical therapy, approximately a third of patients continue taking NSAIDs after adding bDMARD therapy, although often at a reduced dose. This may reflect an insufficient or ineffective immunosuppressive therapy, residual symptoms that still require occasional NSAID use or perhaps non-inflammatory pain mechanisms such as fibromyalgia. Furthermore, NSAID use may even reflect concomitant or secondary degenerative joint disease. Addressing this pain may require a multidisciplinary approach and there are still benefits with patient education and physiotherapy.[140, 141]

Coverage of registries

Real-world, prospectively collected registries for assessing the effectiveness of DMARD therapy have been established or implemented at most rheumatology clinics worldwide. They have proven themselves indispensable in evaluating treatment effectiveness and provide the physician and other health-care workers with registration and calculations of composite scores to indicate the activity of several rheumatic diseases. They have proven important in keeping a bird's-eye view over the treatment of patients with rheumatic joint disease, when trying to visualise the treatment which has taken place over many years or decades, and find trends or signals that may assist in choosing the right course of action or deciding when to intervene. They assist in combating the saying from Verna Wright, MD stated in the beginning of this thesis: *"Clinicians may all too easily spend years writing 'doing well' in the notes of a patient who has become progressively crippled before their eyes."*

The data from the registries used for this thesis, SRQ and ICEBIO, both have the strength of national coverage. The value of registries depends on their completeness and regular complete registrations are the key to performing proper post-marketing evaluations of a rapidly growing pharmaceutical market, as well as to observe disease activity and treatment effectiveness trends in both the population and in the individual patient. They can tell us how the disease has progressed over the years, whether it has remained relatively stable, and which therapeutic interventions have been tried and how they performed.

The main limitation of registry-based studies, and inherent limitation to all four studies in this thesis, is missing data. This specifically applies to patient-reported outcomes and domains of disease, other than joints. Both registries used in this thesis have excellent quality. SRQ is a large registry with a coverage that exceeds 90% of patients receiving biologic therapy for PsA in Sweden, supported by electronic reporting from 56 rheumatology

units. ICEBIO is a smaller registry with over 98% coverage, and in some studies, manual collection of additional data is frequently possible.

Despite being firmly incorporated into clinical practice, missing data in our study was up to a third of values in some of the more common variables, and in some cases up to 95% (for example axial scores or enthesitis indices). In research studies based on registries, multiple data imputations are usually necessary.[142-145] Nevertheless, it is important to keep registrations incorporated into clinical care, use manual validation to complete missing registrations, tie the use of biologics to a registration requirement, as in Iceland, and continue to let registries reward both physicians and patients for their use of registries. Registries help physicians gain quick access to a bird's-eye view and rapid calculation of disease activity scores (Appendices B and C). They can be further supplemented to flag patients when they require other interventions such as rehabilitation or physiotherapy. For patients it can provide a more hands-on insight into the disease process and encourage their active participation in choosing and following up treatment goals.

Limitations of registry-based studies

Registry studies provide unique opportunities to investigate real-world effectiveness, safety and long-term outcomes in unselected populations. However, there are several limitations that must be acknowledged when interpreting the findings of this thesis.

Both the ICEBIO and SRQ registries have excellent coverage of patients with PsA in Iceland and Sweden, but there is significant missing or incomplete data at the visit registration level, which is an important limitation. Missingness is rarely completely at random, it may relate to disease activity (patients doing poorly may be less motivated to register). In this thesis, analyses were based on available data, multiple imputations were performed in Studies III and IV and sensitivity analyses were performed that indicate that the main conclusions were robust despite missing data.

Missing 66/68 joint counts in the earlier registrations likely reflects new approaches in the management of PsA. In the earlier years of both registries there are very few 66/68 joint counts registered, making 28 joint counts the only available data. Laboratory values are sometimes unavailable, especially if they are not automatically transferred between computer systems. Patient reported outcomes are sometimes unavailable even though other parts of the visit registrations took place. This limitation is especially significant in Studies I, III, and IV where we had to rely on disease activity

indicators using only 28 joint counts, which do not capture important disease manifestations in PsA such as enthesitis, axial disease and arthritis of the feet.

Registries are primarily designed for quality monitoring and regular data collection. As a result, some relevant variables are not consistently captured, such as imaging data, detailed skin scoring or socioeconomic factors. Despite these significant limitations, the longitudinal data on a large scale provides valuable insights that may outweigh the limitations in population-based research. Registry-based research remains indispensable to understand treatment effectiveness, drug persistence and remission in a heterogeneous patient population.

Selection of remission criteria

Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy.

EULAR treatment guidelines for psoriatic arthritis recommendation 1

The choice of remission criteria influences estimates of treatment success and the interpretation of sustained remission in registry-based research such as the present thesis. Although the EULAR guidelines state that the treatment goal is remission or low disease activity, it is left to the clinician how to interpret their findings and assess the patient's disease activity. As stated in the background information of this thesis, there are multiple criteria to use when evaluating whether a patient is in remission or has low, moderate or high disease activity. There is no clear consensus on which criteria to use, and they may be differently suited for different scenarios. For example, DAPSA relies heavily on joint manifestations, and while that may be suitable in a patient with mainly symmetrical polyarthritis, it becomes less valuable in oligo- or monoarthritis, axial arthritis or predominantly entheseal or skin disease.

In Study III, we evaluated a range of composite disease activity scores and evaluated those for which we had sufficient data. Since 66/68 joint counts were not routinely implemented until the more recent years, 28 joint counts remain the most consistently available data in older registry entries. Although the 28 joint counts are suboptimal for PsA, particularly as they omit the commonly affected feet, they allow for consistent longitudinal analysis across the whole cohort. Results presented in this thesis rely on

which composite scores were available, i.e. DAPSA28 and DAS28CRP, which is an important limitation of our studies. On the other hand, we included another outcome measure which is the physician assessment of disease activity on a Likert scale of 0-4, mainly due to the high availability in the SRQ and we anticipated that it would capture more disease manifestations.

The 66/68 swollen and tender joint counts and DAPSA are excellent for primarily peripheral arthritis.[146] MDA/VLDA performs very well in most patients and includes skin disease, enthesitis, and physical function making it a strong overall score, although VLDA is very stringent.[78, 146] When treating mainly axial disease the physician may need to borrow from axial spondyloarthritis studies and use BASDAI/BASFI/BASMI.[147]

With continued registrations in biologic registries, we may increasingly incorporate regular assessments of other domains of psoriatic disease into routine care. The registries will continue to evolve and provide more robust and meaningful data so that we can more accurately assess the outcomes we are interested in.

Viability of remission in all patients

In Study III and IV we compare the rates of SR between Iceland and Sweden. We see that there is a slightly higher occurrence of SR in Iceland, and when including data up until June 1st, 2025 we see increasing SR rates from 29% to 33%. Patients who have never experienced remission decrease from 53% to 48%. These numbers may indicate that there is a time trend toward less disease activity and may indicate better inflammation control through increased availability of advanced therapies and improved treatment strategies. EULAR and GRAPPA guidelines recommend setting remission or low disease activity as a treatment goal for all patients which has become the standard treatment target. With improving therapeutics and treatment strategies, SR has reached a rate of 33% and lasted a median of 3,3 years, showing that remission in all patients is becoming an increasingly more realistic treatment goal.

7 – CONCLUSIONS

- Patients who did not meet the inclusion criteria for RCTs of TNF inhibitors achieved treatment responses and drug survival similar to RCT-eligible patients, thereby supporting the external validity of biologic therapy efficacy.
- NSAID use decreased by approximately 40-50% after initiation of a first-line TNF inhibitor in both psoriatic arthritis and other forms of inflammatory arthritis, reflecting improved disease control and a significant indirect benefit of optimal pharmacological treatment.
- Sustained remission lasting at least six months was achieved only by a minority of PsA patients, approximately one in four, when using the more stringent DAPSA28 criterion, and around half when evaluated with DAS28CRP or physician global assessment.
- Male sex and lower baseline swollen joint count consistently predicted sustained remission which highlights the importance of early disease control.
- Data from two national rheumatology registries demonstrate that while biologic therapy delivers meaningful benefits in many patients with PsA, sustained remission remains an ambitious but attainable goal in many patients. To reach this goal, treatment strategies need to be refined and personalised therapy selection needs to be implemented.
- Comprehensive registry-based follow-up provides research with important markers to achieve these goals.

8 - FUTURE CONSIDERATIONS

As in RA, it is likely that achieving early disease control and sustained remission benefits patients with psoriatic arthritis in the long term. Most patients will require long-term DMARD treatment, as the disease carries a high risk of worsening physical function, decreased quality of life, and reduced social and work participation. Early symptoms can be mild for an extended period, which makes early diagnosis challenging. Based on our current knowledge we can envision that in the future:

- Implement strategies for general practitioners to recognise the symptoms of psoriatic arthritis early in patients who may need more active anti-rheumatic treatment and make timely referrals to the rheumatology departments.
- Uitilise advanced diagnostic tools, such as musculoskeletal ultrasound and emerging biomarkers, to enhance diagnostic accuracy.
- Explore the long-term advantages of sustained remission.
- Use personalised or precision medicine to choose therapy tailored to the individual patient.
- Explore the possibility of dose reduction and the achievement and maintenance of drug-free remission.
- Develop diagnostic tools for the early identification of patients with concomitant chronic pain or fibromyalgia, and implement strategies to address these conditions.
- Enhance the screening and management of obesity, metabolic syndrome, and cardiovascular disease. Improve management of concomitant fibromyalgia and degenerative joint disease, and more accurately assess the activity of psoriatic arthritis in the presence of comorbidities.
- Maintain and improve contributions to registries with a more comprehensive 66/68 joint counts and assessments of skin, axial and entheseal disease to then accurately be able to follow trends in the frequency of sustained remission.

Possibly in the future, we will develop a method to identify patients at risk for psoriatic arthritis based on genetic or environmental factors, as well as

possible emerging biomarkers and ultimately prevent the disease. Until then, we will continue striving to reach and maintain remission in all patients with psoriatic arthritis.

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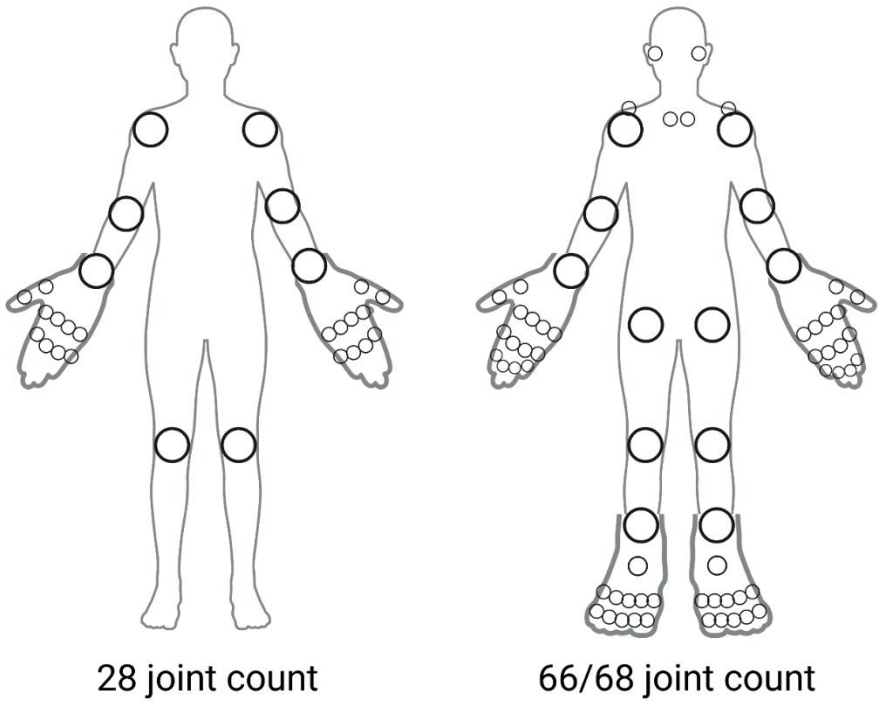
11 – LIST OF APPENDICES

A. 28 and 66/68 joint scoring sheet
B. ICEBIO interface
C. SRQ interface
D. Patient paper form for ICEBIO registration

Appendix A

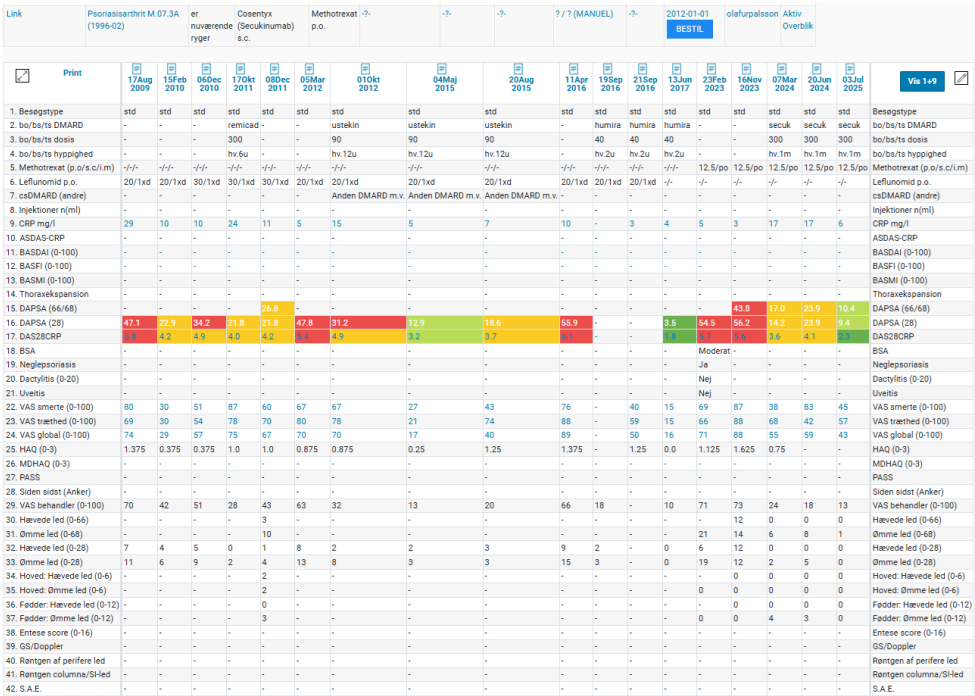
28 and 66/68 joint scoring sheet



Scoring sheet for 28 and 66/68 joint counts. Mark \ for tender, / for swollen, X if both. Created in BioRender. Pálsson, Ó. (2025) https://BioRender.com/mw8twdu

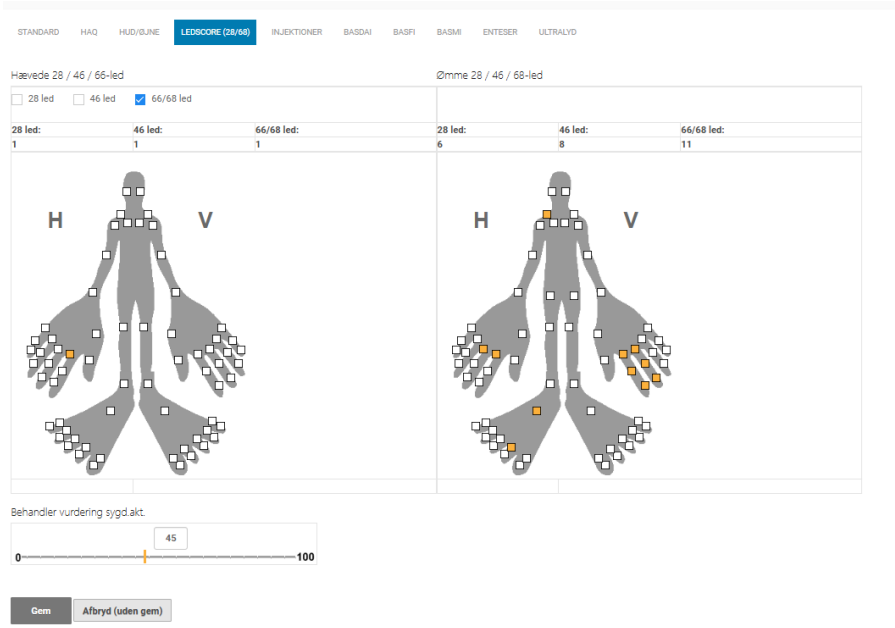
Appendix B

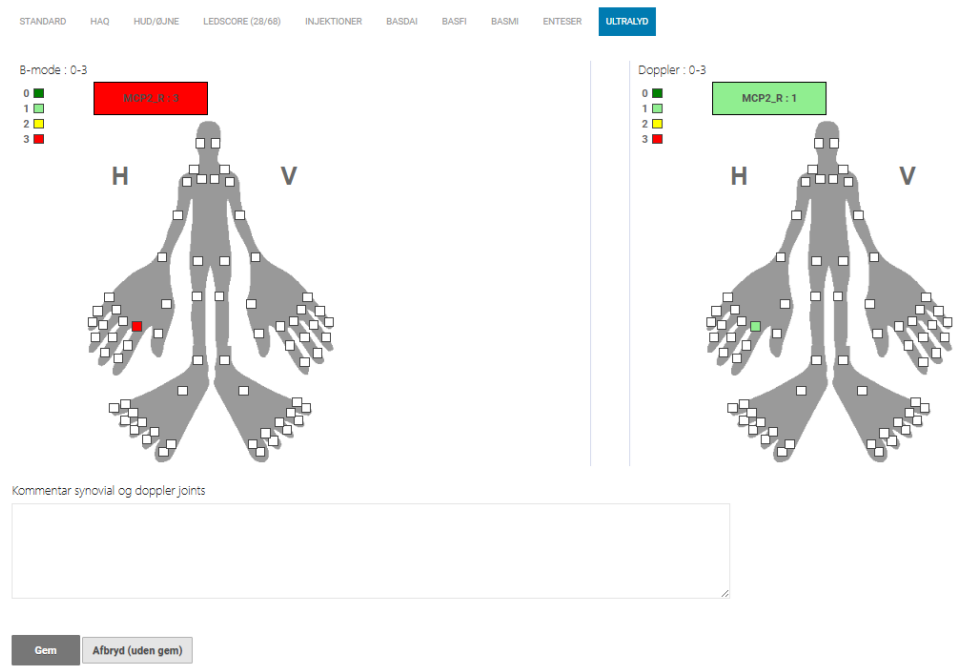
ICEBIO data entry form and treatment overview screen



Link	Psoriasisarthrit M.07.3A (1996-02)	er nuværende ryger	Cosentyx (Secukinumab) s.c.	Methotrexat p.o.	-?-	-?-	-?-	? / ? (MANUEL)	-?-	2012-01-01 BESTIL	olafurpalsson	Aktiv Overblik

Print	17Aug 2009	15Feb 2010	06Dec 2010	17Okt 2011	08Dec 2011	05Mar 2012	01Okt 2012	04Maj 2015	20Aug 2015	11Apr 2016	19Sep 2016	21Sep 2016	13Jun 2017	23Feb 2023	16Nov 2023	07Mar 2024	20Jun 2024	03Jul 2025	Vis 1-9
1. Besøgstype	std	std	std	std	std	std	std	std	std	std	std	std	std	std	std	std	std	std	Besøgstype
2. bo/bs/ts DMARD	-	-	-	remicad	-	-	ustekin	ustekin	ustekin	-	humira	humira	humira	-	-	secuk	secuk	secuk	bo/bs/ts DMARD
3. bo/bs/ts dosis	-	-	-	300	-	-	90	90	90	-	40	40	40	-	-	300	300	300	bo/bs/ts dosis
4. bo/bs/ts hyppighed	-	-	-	hv.6u	-	-	hv.12u	hv.12u	hv.12u	-	hv.2u	hv.2u	hv.2u	-	-	hv.1m	hv.1m	hv.1m	bo/bs/ts hyppighed
5. Methotrexat (p.o/s.c/i.m)	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	12.5/po	12.5/po	12.5/po	12.5/po	12.5/po	Methotrexat (p.o/s.c/i.m)
6. Leflunomid p.o.	20/1xd	20/1xd	30/1xd	30/1xd	30/1xd	20/1xd	20/1xd	20/1xd	20/1xd	20/1xd	20/1xd	20/1xd	-/-	-/-	-/-	-/-	-/-	-/-	Leflunomid p.o.
7. csDMARD (andre)	-	-	-	-	-	-	Anden DMARD m.v.	Anden DMARD m.v.	Anden DMARD m.v.	-	-	-	-	-	-	-	-	-	csDMARD (andre)
8. Injektioner n(ml)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Injektioner n(ml)
9. CRP mg/l	29	10	10	24	11	5	15	5	7	10	-	3	4	5	3	17	17	6	CRP mg/l
10. ASDAS-CRP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	ASDAS-CRP
11. BASDAI (0-100)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	BASDAI (0-100)
12. BASFI (0-100)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	BASFI (0-100)
13. BASMI (0-100)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	BASMI (0-100)
14. Thoraxekspansion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Thoraxekspansion
15. DAPSA (66/68)	-	-	-	-	26.8	-	-	-	-	-	-	-	-	-	43.8	17.0	23.9	10.4	DAPSA (66/68)
16. DAPSA (28)	47.1	22.9	34.2	21.8	21.8	47.8	31.2	12.9	18.6	55.9	-	-	3.5	54.5	56.2	14.2	23.9	9.4	DAPSA (28)
17. DAS28CRP	5.8	4.2	4.9	4.0	4.2	6.4	4.9	3.2	3.7	6.1	-	-	1.8	3.7	5.6	3.6	4.1	2.3	DAS28CRP
18. BSA	-	-	-	-	-	-	-	-	-	-	-	-	-	Moderat	-	-	-	-	BSA
19. Neglepsoriasis	-	-	-	-	-	-	-	-	-	-	-	-	-	Ja	-	-	-	-	Neglepsoriasis
20. Dactylitis (0-20)	-	-	-	-	-	-	-	-	-	-	-	-	-	Nej	-	-	-	-	Dactylitis (0-20)
21. Uveitis	-	-	-	-	-	-	-	-	-	-	-	-	-	Nej	-	-	-	-	Uveitis
22. VAS smerte (0-100)	80	30	51	87	60	67	67	27	43	76	-	40	15	69	87	38	83	45	VAS smerte (0-100)
23. VAS træthed (0-100)	69	30	54	78	70	80	78	21	74	88	-	59	15	66	88	68	42	57	VAS træthed (0-100)
24. VAS global (0-100)	74	29	57	75	67	70	70	17	40	89	-	50	16	71	88	55	59	43	VAS global (0-100)
25. HAQ (0-3)	1.375	0.375	0.375	1.0	1.0	0.875	0.875	0.25	1.25	1.375	-	1.25	0.0	1.125	1.625	0.75	-	-	HAQ (0-3)
26. MDHAQ (0-3)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	MDHAQ (0-3)
27. PASS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	PASS
28. Siden sidst (Anker)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Siden sidst (Anker)
29. VAS behandler (0-100)	70	42	51	28	43	63	32	13	20	66	18	-	10	71	73	24	18	13	VAS behandler (0-100)
30. Hævede led (0-66)	-	-	-	-	3	-	-	-	-	-	-	-	-	-	12	0	0	0	Hævede led (0-66)
31. Ømme led (0-68)	-	-	-	-	10	-	-	-	-	-	-	-	-	21	14	6	8	1	Ømme led (0-68)
32. Hævede led (0-28)	7	4	5	0	1	8	2	2	3	9	2	-	0	6	12	0	0	0	Hævede led (0-28)
33. Ømme led (0-28)	11	6	9	2	4	13	8	3	3	15	3	-	0	19	12	2	5	0	Ømme led (0-28)
34. Hoved: Hævede led (0-6)	-	-	-	-	2	-	-	-	-	-	-	-	-	-	0	0	0	0	Hoved: Hævede led (0-6)
35. Hoved: Ømme led (0-6)	-	-	-	-	2	-	-	-	-	-	-	-	-	0	0	0	0	0	Hoved: Ømme led (0-6)
36. Fødder: Hævede led (0-12)	-	-	-	-	0	-	-	-	-	-	-	-	-	-	0	0	0	0	Fødder: Hævede led (0-12)
37. Fødder: Ømme led (0-12)	-	-	-	-	3	-	-	-	-	-	-	-	-	0	0	4	3	0	Fødder: Ømme led (0-12)
38. Entese score (0-16)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Entese score (0-16)
39. GS/Doppler	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	GS/Doppler
40. Røntgen af perifere led	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Røntgen af perifere led
41. Røntgen columna/SI-led	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Røntgen columna/SI-led
42. S.A.E.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S.A.E.


STANDARD
HAQ
HUD/ØJNE
LEDSCORE (28/68)
INJEKTIONER
BASDAI
BASFI
BASMI
ENTESER
ULTRALYD
Hævede 28 / 46 / 66-led
28 led
46 led
66/68 led
28 led:
46 led:
66/68 led:
1
1
1
Ømme 28 / 46 / 68-led
28 led:
46 led:
66/68 led:
6
8
11
H
V
H
V
Behandler vurdering sygd.akt.
45
0
100
Gem
Afbryd (uden gem)


STANDARD
HAQ
HUD/ØJNE
LEDSCORE (28/68)
INJEKTIONER
BASDAI
BASFI
BASMI
ENTESER
ULTRALYD
B-mode : 0-3
0
1
2
3
MCP2_R : 3
H
V
Doppler : 0-3
0
1
2
3
MCP2_R : 1
H
V
Kommentar synovial og doppler joints
Gem
Afbryd (uden gem)

	0	1	2	3
Klæde Dem på [MDHAQ]?	☑	☐	☐	☐
Vaske Deres hår?	☑	☐	☐	☐
Rejse Dem fra en spisestuestol?	☑	☐	☐	☐
Klare at komme i og ud af en seng [MDHAQ]?	☑	☐	☐	☐
Skære et stykke stegt kød i stykker?	☑	☐	☐	☐
Løfte en fyldt kop eller et fyldt glas [MDHAQ]?	☑	☐	☐	☐
Åbne en ny mælkekarton?	☐	☑	☐	☐
Gå rundt udendørs, hvor der er fladt [MDHAQ]?	☑	☐	☐	☐
Gå 5 trin op ad en trappe?	☑	☐	☐	☐
Vaske og tørre Dem over det hele [MDHAQ]?	☑	☐	☐	☐
Tage karbad?	☑	☐	☐	☐
Klare toiletbesøg?	☑	☐	☐	☐

	0	1	2	3
Hente noget tungt over hovedhøjde?	☑	☐	☐	☐
Samle feks. tøj op fra gulvet [MDHAQ]?	☑	☐	☐	☐
Åbne en bildør?	☑	☐	☐	☐
Skrue låget af et åbnet glas?	☑	☐	☐	☐
Åbne og lukke en vandhane [MDHAQ]?	☑	☐	☐	☐
Klare indkøb og andre ærinder?	☑	☐	☐	☐
Komme ind og ud af en bil [MDHAQ]?	☐	☑	☐	☐
Klare husarbejdet?	☐	☐	☑	☐
Gå 3 kilometer, hvis du ville (den seneste uge) [MDHAQ]	☐	☐	☐	☐
Deltage i fritidsaktiviteter og sport, som du synes om, hvis du ville (den seneste uge) [MDHAQ]	☐	☐	☐	☐
Få en god nats søvn (den seneste uge)	☐	☐	☐	☐
Håndtere følelse af ængstelse eller nervøsitet (den seneste uge). Hvis du ikke har følt dig ængstelig eller nervøs, besvares spørgsmålet Ja, uden besvær.	☐	☐	☐	☐
Håndtere følelse af depression eller tristhed (den seneste uge). Hvis du ikke har følt dig depressiv eller trist, besvares spørgsmålet Ja, uden besvær	☐	☐	☐	☐

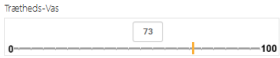
HAQ-score(papirskema)

MDHAQ-score(papirskema)

INFO: Smerte-VAS (0 = Ingen gigtsmerter, 100 = Uudholdelige gigtsmerter), Trætheds-VAS og Global-VAS (0 = Slet ikke, 100 = Uudholdeligt meget)

Smerte-VAS

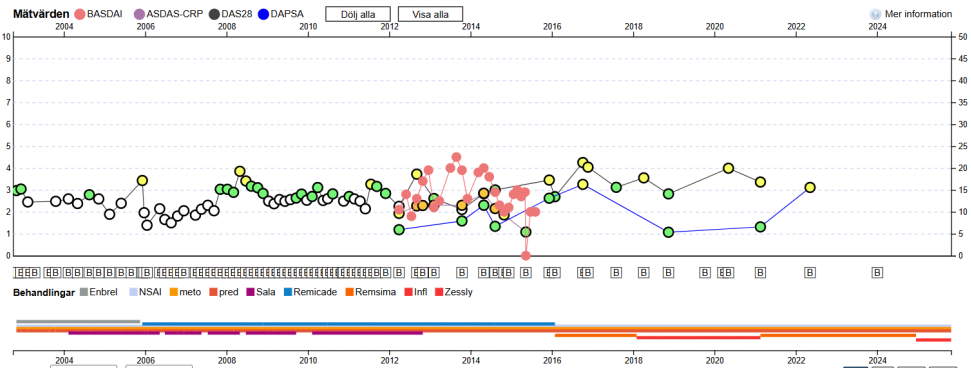
Trætheds-Vas



Global-VAS

Appendix C

SRQ data entry form and treatment overview screen


Mätvärden
BASDAI
ASDAS-CRP
DAS28
DAPSA
Dölj alla
Visa alla
Mer information
Behandlingar
Enbrel
NSAI
meto
pred
Sala
Remicade
Remsima
Infl
Zessly

Appendix D

Patient reported outcome measures, pain, fatigue and global health VAS and HAQ questionnaire

Spurningum hér að neðan er svarað á sjónskala með því að **draga línu yfir strikið** við hverja spurningu. Dæmi:

Gott ——— Slæmt

Verkur (VAS Pain)

Settu strik á línuna hér að neðan sem lýsir verkjum sem sjúkdómur þinn veldur **síðastliðna viku**

Enginn verkur ——— Óbærilegir verkir

Þreyta (VAS Fatigue)

Settu strik á línuna hér að neðan sem lýsir þreytu sem sjúkdómur þinn veldur **síðastliðna viku**

Engin þreyta ——— Óbærileg þreyta

Sjúkdómsvirkni (VAS Global)

Hvert er þitt mat á sjúkdómsvirkni **síðastliðna viku**

Mjög góð líðan
Engin óþægindi ——— Mjög mikil vanlíðan
Mikil óþægindi

Spurningakver um heilsutengd lífsgæði (HAQ)

Við viljum athuga hvaða áhrif sjúkdómur þinn hefur á færni þína til athafna daglegs lífs. Setu kross við það svar sem best lýsir ástandi þínu **síðustu viku**. Krossaðu við það svar sem best á við.

	Auðveldlega	Með nokkrum erfiðismunum	Með miklum erfiðismunum	Get það ekki
Klæðnaður og snyrting				
Getur þú -				
1. klætt þig, hnýtt skóreimar og hneppt hnöppum?	☐	☐	☐	☐
2. þvegið á þér hárið?	☐	☐	☐	☐
Fótaferð				
Getur þú -				
3. staðið upp úr stól sem ekki hefur arma?	☐	☐	☐	☐
4. farið upp í og fram úr rúmi?	☐	☐	☐	☐

Snúið blaðinu við

GIGTARMIÐSTÖÐIN

	Auðveldlega	Með nokkrum erfiðismunum	Með miklum erfiðismunum	Get það ekki
Máltíðir				
Getur þú -				
5. skorið kjöt á diski?	☐	☐	☐	☐
6. lyft fullu glasi eða bolla að munni?	☐	☐	☐	☐
7. opnað mjólkurfernu eða fernu með ávaxtasafa í?	☐	☐	☐	☐
Ganga				
Getur þú -				
8. gengið á sléttri grund (flatlendi) utanhúss?	☐	☐	☐	☐
9. gengið upp fimm tröppur (þrep)?	☐	☐	☐	☐
Hreinlæti				
Getur þú -				
10. þvegið og þurrkað allan líkamann?	☐	☐	☐	☐
11. baðað þig í baðkeri?	☐	☐	☐	☐
12. sest á og staðið upp af salerni?	☐	☐	☐	☐
Seiling				
Getur þú -				
13. tekið tveggja kílógramma poka, t.d. af sykri úr hillu sem er yfir höfuðhæð?	☐	☐	☐	☐
14. beygt þig niður og tekið föt up af gólfi?	☐	☐	☐	☐
Gripgeta				
Getur þú -				
15. opnað hurð á bíl?	☐	☐	☐	☐
16. skrúfað lok af sultukrukku, sem þegar hefur verið opnuð?	☐	☐	☐	☐
17. skrúfað frá og fyrir vatnskrana?	☐	☐	☐	☐
Annað				
Getur þú -				
18. farið í búðir og keypt inn fyrir heimilið?	☐	☐	☐	☐
19. komist inn og út úr bíl?	☐	☐	☐	☐
20. sinnt heimilisstörfum?	☐	☐	☐	☐
	0	1	2	3

Stig	1	2	3	4	5	6	7	8	9	10	11	12
HAQ	0,125	0,25	0,375	0,5	0,625	0,75	0,875	1	1,125	1,25	1,375	1,5
Stig	13	14	15	16	17	18	19	20	21	22	23	24
HAQ	1,625	1,75	1,875	2	2,125	2,25	2,375	2,5	2,625	2,75	2,875	3

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