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Dose Reduction of Biological Therapies in Patients with Inflammatory Arthritis

Maintaining Stable Disease Activity on Reduced Dose

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MAINTAINING STABLE DISEASE ACTIVITY ON REDUCED DOSE

BY
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DENMARK

DOSE REDUCTION OF BIOLOGICAL THERAPIES IN PATIENTS WITH INFLAMMATORY ARTHRITIS

MAINTAINING STABLE DISEASE ACTIVITY ON REDUCED DOSE

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Dissertation submitted 2022

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Academic degree
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PhD Student, Faculty of Medicine, Aalborg University.

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Leave of absence from PhD to enrol participants in the
BIODOPT trial during Rheumatology fellowship, Aalborg University Hospital.

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PhD Student, Faculty of Medicine, Aalborg University.

Research fields
Main research areas are patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) with focus on the possibility to reduce dose of biological therapies while maintain stable disease activity. Furthermore, validation and national implementation of the DANBIO app in patients with RA, PsA and axSpA as well as patients with systemic lupus erythematosus. Moreover, participation in various collaborative research trials both nationally and internationally.

Teaching experience
Since 2016, participated in the education of medical students and biomedical students from Aalborg University. Moreover, educational presentation for health care professionals about rheumatic diseases at several occasions.

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Board member of the Committee for National Treatment Guidelines since 2017. Head of the Danish National Guideline on rheumatic drugs since January 2022. Participated on the following Danish National Guidelines:
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- Treatment guideline and patient information for rheumatic drugs
- Guideline on the management of pregnancy, lactation and male reproduction in patients with rheumatic diseases
- Guideline on cardiovascular risk in patient with inflammatory arthritis
- Guideline on osteoporosis risk in patient with inflammatory arthritis

Publications (not included in this thesis)

Uhrenholt L, Christensen R, Dreyer L, Schlemmer A, Hauge EM, Krogh NS, Abildtoft MK, Taylor PC, Kristensen S. Using a novel smartphone application for capturing of patient-reported outcome measures among patients with inflammatory arthritis: A randomized, crossover, agreement study. *Scand J Rheumatol 2022;51:25-33.*

Eriksen TE, Dinesen WKH, **Uhrenholt L**, Dreyer L, Duch K, Kristensen S. Isolation in patients with inflammatory rheumatic diseases during COVID-19 pandemic compared to healthy individuals: A questionnaire survey. *Rheumatol Int 2022;42:783-790.*

Hetland ML, Haavardsholm E, Rudin A, Nordström D, Nurmohamed M, Gudbjornsson B, Lampa J, Hørslev-Petersen K, Uhlig T, Grondal G, Østergaard M, Heiberg M, Twisk J, Lend K, Krabbe S, Hyldstrup LH, Lindqvist J, Ekwall A, Lederballe Grøn K, Kapetanovic M, Faustini F, Tuompo R, Lorenzen T, Cagnotto G, Baecklund E, Hendricks O, Vedder D, Sokka-Isler T, Husmark T, Ljoså M, Brodin E, Ellingsen T, Söderbergh A, Rizk M, Reckner Å, Larsson P, **Uhrenholt L**, Just S, Stevens D, Laurberg T, Bakland G, Olsen I, van Vollenhoven R, NORD-STAR study group. Active conventional treatment and three different biological treatments in early rheumatoid arthritis: phase IV investigator initiated, randomised, observer blinded clinical trial. *BMJ 2020;371:m4328.*

Uhrenholt L, Høstgaard S, Pedersen JF, Christensen R, Dreyer L, Leffers HCB, Taylor PC, Strand V, Jacobsen S, Voss A, Gregersen JW, Kristensen S. Patient-reported outcome measures in systemic lupus erythematosus by a web-based application: A randomized, crossover, agreement study. *Lupus 2021;30:2124-2134.*

Cordtz R, Lindhardsen J, Soussi BG, Vela J, **Uhrenholt L**, Westermann R, Kristensen S, Nielsen H, Torp-Pedersen C, Dreyer L. Incidence and severeness of COVID-19 hospitalisation in patients with inflammatory rheumatic disease: a nationwide cohort study from Denmark. *Rheumatology (Oxford) 2021;60:S159-S167*

Uhrenholt L, Jensen LS, Jakobsen TS, Kristensen S, Dahlerup JF, Pahle E, Nielsen MF. [Acute abdominal vasculitis in rheumatic diseases]. *Ugeskr Laeger. 2018;180: V05170419.*

Conference abstracts

Uhrenholt L, Christensen R, Dreyer L, Hauge EM, Schlemmer A, Loft AG, Rasch MNB, Horn HC, Gade K, Taylor PC, Kristensen S. Disease activity-guided tapering of biologics in patients with inflammatory arthritis: A randomised, open-label, equivalence trial. *Annals of the Rheumatic Diseases 2022 (Ahead of print:OP0022)*

Østergaard M, van Vollenhoven R, Rudin A, Lund Hetland M, Heiberg M, Nordström D, Nurmohamed M, Gudbjornsson B, Ørnbjerg LM, Bøyesen P, Olsen I, Lend K, Hørslev-Petersen K, Uhlig T, Sokka-Isler T, Grondal G, Krabbe S,

Lindqvist J, Gjertsson I, Glinatsi D, Kapetanovic MC, Aga AB, Faustini F,Parmanne P, Lorenzen T, Cagnotto G, Back J, Hendricks O, Vedder D, Rannio T, Grenholm E, Lindegaard HM, Ljosa MKA, Brodin E, Söderbergh A, Rizk M, Hermannson E, **Uhrenholt L**, *Larsson P, Just S, Bakland G, Stevens D, Laurberg T, Haavardsholm E, Lampa J.* Certolizumab-pegol, abatacept, tocilizumab or active conventional therapy in early rheumatoid arthritis: Clinical and radiographic 48-weeks results of the investigator-initiated randomized NORD-STAR trial. *Annals of the Rheumatic Diseases 2022 (Ahead of print: OP0058)*

Uhrenholt L, *Christensen R, Dinesen WK, Liboriussen C, Andersen S, Dreyer L, Schlemmer A, Hauge EM, Skrubbeltrang C, Kristensen S.* Tapering and Withdrawal of Biologics or Targeted Synthetic Disease-Modifying Antirheumatic Drugs in Patients with Inflammatory Arthritis: A Systematic Review and Meta-Analyses of Randomised Trials. *Arthritis Rheumatol 2021;73:S10:1710-1713.*

Uhrenholt L, *Høstgaard S, Pedersen JF, Christensen R, Dreyer L, Leffers HCB, Taylor PC, Strand V, Jacobsen S, Voss A, Gregersen JW, Kristensen S.* Digital Solution for Collection of Patient-reported Outcome Measures in Patients with Systemic Lupus Erythematosus: A Randomised, Crossover, Agreement Study. *Arthritis Rheumatol 2021;73:S10:2636-2639.*

Østergaard M, van Vollenhoven R, Rudin A, Lund Hetland M, Heiberg M, Nordström D, Nurmohamed M, Gudbjornsson B, Ørnbjerg LM, Bøyesen P, Olsen I, Lend K, Hørslev-Petersen K, Uhlig T, Sokka-Isler T, Grondal G, Krabbe S, Lindqvist J, Gjertsson I, Glinatsi D, Kapetanovic MC, Aga AB, Faustini F,Parmanne P, Lorenzen T, Cagnotto G, Back J, Hendricks O, Vedder D, Rannio T, Grenholm E, Lindegaard HM, Ljosa MKA, Brodin E, Söderbergh A, Rizk M, Hermannson E, **Uhrenholt L**, *Larsson P, Just S, Bakland G, Stevens D, Laurberg T, Haavardsholm E, Lampa J.* An Investigator-initiated Multicenter Randomized Study in Early Rheumatoid Arthritis of Active Conventional Therapy versus Three Biological Treatments: 48 Week Clinical and Radiographic Results of the NORD-STAR Trial. *Arthritis Rheumatol 2021;73:S10:1701-1705.*

Uhrenholt L, *Christensen R, Dreyer L, Schlemmer A, Hauge EM, Krogh NS, Abildtoft MK, Taylor PC, Kristensen S.* Agreement between patient-reported outcome measures collected via a smartphone application vs a touchscreen solution in an outpatient clinic among patients with inflammatory arthritis: A randomised, within-participant trial. *Annals of the Rheumatic Diseases 2020;79:S1:1919-1920.*

Hetland ML, Haavardsholm E, Rudin A, Nordström D, Nurmohamed M, Gudbjornsson B, Lampa J, Hørslev-Petersen K, Uhlig T, Grondal G, Østergaard M, Heiberg M, Twisk J, Krabbe S, Lend K, Olsen I, Lindqvist J, Ekwall A, Lederballe Grøn K, Kapetanovic M, Faustini F, Tuompo R, Lorenzen T, Cagnotto G, Baecklund E, Hendricks O, Vedder D, Sokka-Isler T, Husmark T, Ljoså M, Brodin E, Ellingsen T, Söderbergh A, Rizk M, Reckner Å, Larsson P, **Uhrenholt L**, *Just S, Stevens D, Laurberg T, Bakland G, van Vollenhoven R.* A multicenter randomized study in

early rheumatoid arthritis to compare active conventional therapy versus three biological treatments: 24 week efficacy results of the nord-star trial. *Annals of the Rheumatic Diseases 2020;79:S1:13-14.*

Glintborg B, Hendricks O, Colic A, Lindegaard HM, Ahmed R, Loft AG, Kollerup G, Andersen M, Grydehøj J, Raun J, Thorgrimsen T, Mortensen K, **Uhrenholt L***, Jensen D, Ruge I, Kalisz M, Danebod K, Lomborg N, Krogh NS, Hetland ML.* Treat-to-target strategy of >8.000 patients with early rheumatoid arthritis: Does smoking affect achievement of remission on methotrexate and time to start of first biologic? Results from the nationwide danish danbio registry. *Annals of the Rheumatic Diseases 2020;79:S1:1001-1002.*

Hetland ML, Haavardsholm E, Rudin A, Nordström D, Nurmohamed M, Gudbjornsson B, Lampa J, Hørslev-Petersen K, Uhlig T, Grondal G, Østergaard M, Heiberg M, Twisk J, Lend K, Krabbe S, Lindqvist J, Ekwall A, Lederballe Grøn K, Kapetanovic M, Faustini F, Tuompo R, Lorenzen T, Cagnotto G, Baecklund E, Hendricks O, Vedder D, Sokka-Isler T, Husmark T, Ljoså M, Brodin E, Ellingsen T, Söderbergh A, Rizk M, Reckner Å, **Uhrenholt L***, Larsson P, Just S, Stevens D, Laurberg T, Bakland G, Olsen I, van Vollenhoven R.* A multicenter randomized study in early rheumatoid arthritis to compare active conventional therapy versus three biological treatments: 24 week efficacy and safety results of the NORD-star trial. *Arthritis Rheumatol;2019:S10:5237-5240.*

Poster award

Received the award for best poster presentation (on study I from this thesis) at the Danish Society of Rheumatology annual meeting in 2021.

ENGLISH SUMMARY

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) are characterised by peripheral and/or axial inflammatory joint disease and possible extra-articular manifestations. The term inflammatory arthritis (IA) is often used to describe the three chronic joint diseases.

The management of IA have significantly improved over the last decades due to increased focus on disease activity-guided monitoring and enhanced treatment options including biologic and targeted synthetic disease modifying anti-rheumatic drugs (b-/tsDMARDs, respectively). As the majority of patients with IA now can reach sustained remission or low disease activity (LDA), a relevant question is if the therapies should be continued at standard dose indefinitely.

In recent years, dose reduction of biological therapies has been evaluated in some clinical trials with the majority in RA, less in axSpA and fewer trials in PsA. Data have shown an increased risk for loss of LDA with biologics withdrawal compared to continuation of standard dose; therefore, the strategy is generally judged to be inferior. Another dose reduction strategy is tapering i.e. biologic dose reduction or interval prolongation which can be done in one fixed step (e.g. 50% dose reduction) or gradually over time by a disease activity-guided algorithm until flare or complete drug withdrawal. The disease activity-guided tapering strategy is considered to be the most aggressive as it allows maximal tapering of biologics. Based the available evidence, biologic tapering seem to be comparable to continuation of standard dose in maintaining stable disease activity. However, only few trials have evaluated disease activity-guided tapering of which the majority had an RA treated with adalimumab or etanercept. Thus, evidence on other biological drugs as well as other diagnose than RA, e.g. PsA or axSpA, is lacking.

This thesis is based on three studies evaluating different aspects of biologic dose reduction in patients with IA in sustained remission or LDA compared to continuation of biologic standard dose.

Study I was a systematic literature review and meta-analysis based on RCTs with an IA study population in sustained remission/LDA on b-/tsDMARDs. The study aimed to evaluate the flare risk when b-/tsDMARDs were tapered or withdrawn compared to standard dose continuation. No RCTs with a PsA study population were identified. Tumour necrosis factor inhibitor (TNFi) withdrawal compared to standard dose continuation was proven to have a highly increased risk for flare and persistent flare whereas b-/tsDMARDs tapering versus standard dose continuation only demonstrated a significantly increased risk for flare and not for persistent flare. Moreover, a highly increased risk for flare and persistent flare was observed when comparing withdrawal to tapering in a network meta-analysis.

Study II was an 18-month long pragmatic, randomised, open-label, equivalence trial aiming to investigate if disease activity-guided tapering could reduce the biologic dose significantly while maintaining stable disease activity compared to continuation of biologics as usual care. One-hundred-and-forty-two patients with IA in sustained LDA on stable dose biologics during ≥12 months were enrolled and randomised. The tapering group prolonged the biologic dosing interval after a disease activity-guided algorithm until flare or drug withdrawal whereas the continuation group maintained baseline biologics but, per patient request, allowed a minor increase in the dosing interval. At 18-months, disease activity between the two trial groups were equivalent despite significantly more patients in the tapering group received ≤50% of their baseline biologic dose compared to the continuation group. Thus, the results from this trial can be used to qualify the discussion of dose reduction in daily clinical practice between the patient and the physician.

Study III aimed to explore if potential predictors for successful tapering of biologics could be identified from baseline characteristics in secondary analyses on data from Study II (the BIODOPT trial). At 18 months follow-up, one third of patients in the tapering group had achieved successful tapering of their biological therapy. A multivariable regression analysis identified better baseline mental health as a potentially important non-significant predictor. Nonetheless, caution must be applied when evaluating the trial results as future research is needed to provide additional insight into possible predictors across IA diagnoses. However, based on this study patient-reported outcome measures (PROMs) such as Short Form 36 (SF-36) seems to provide additional insight to the physician and the patient when tapering is considered.

After evaluation of possible benefits and harms to dose reduction of biological therapies, this thesis demonstrated that tapering should be considered over withdrawal in patients with IA in sustained remission or LDA. Disease activity-guided tapering of biologics in patients with IA was proven to allow significantly more patients in the tapering group to achieve ≥50% dose reduction while an equivalent disease activity state between trial groups was maintained. Better baseline mental health was the only potentially important predictor for successful tapering of biologics.

DANSK RESUME

Leddegigt, psoriasisgigt og rygsøjlegigt er kroniske, inflammatoriske gigtsygdomme som karakteriseres ved perifer ledhævelse og/eller aksial gigtaktivitet eventuelt ledsaget af ekstra-artikulære manifestationer.

Over de seneste årtier er behandlingen af leddegigt, psoriasisgigt og rygsøjlegigt markant forbedret grundet tæt opfølgning, med fokus på at opnå lav sygdomsaktivitet, samt nye behandlingsmuligheder fx biologiske og syntetisk targeterede lægemidler. Da størstedelen af patienter med leddegigt, psoriasisgigt eller rygsøjlegigt nu kan opnå acceptabel ro i gigten, er det relevant at stille spørgsmål ved, om behandling med biologiske eller syntetisk targeterede lægemidler skal forsætte i standard dosis livslangt.

I de seneste år er dosisreduktion af biologisk behandling undersøgt i kliniske studier, hvoraf størstedelen omhandler leddegigt, færre rygsøjlegigt og få psoriasisgigt. Data har påvist risiko for øget gigtaktivitet hvis biologisk behandling stoppes abrupt i forhold til fortsættelse af standard dosis. Derfor anses abrupt ophør med biologisk medicin generelt for at være en mindre anvendelig behandlingsstrategi. En anden strategi er dosisnedtrapning, hvor dosis af den biologiske behandling reduceres eller dosisintervallet forlængelse ved én fastlagt justering (fx 50% dosisreduktion) eller gradvis nedtrapning via en algoritme guidet efter sygdomsaktivitet indtil opblussen i gigten eller total ophør med den biologiske medicin. Af de to anses den algoritmebaseret dosisnedtrapning for at være den mest aggressive strategi, da den sikrer maximal mulig dosisreduktion. Baseret på den nuværende evidens synes dosisnedtrapning at være sammenlignelig med fortsættelse af standard dosis biologisk medicin til at fastholde stabil sygdomsaktivitet. Dog er algoritmebaseret dosisnedtrapning af biologisk medicin guidet efter sygdomsaktivitet kun undersøgt få studier, hvor majoriteten havde en studiepopulation af patienter med leddegigt i behandling med adalimumab eller etanercept. Således er der begrænset evidens for andre biologiske lægemidler samt andre inflammatoriske gigtdiagnoser fx psoriasisgigt og rygsøjlegigt.

Denne afhandling er baseret på tre studier omhandlende dosisreduktion af biologisk behandling versus fortsættelse af standard dosis hos patienter med leddegigt, psoriasisgigt eller rygsøjlegigt med langvarig ro i gigten.

Studie I er et systematisk litteratur review og metaanalyse baseret på randomiserede, kontrollerede studier med en studiepopulation leddegigt, psoriasisgigt eller rygsøjlegigt med langvarig ro i gigten. Studiets formål var at undersøge risikoen for opblussen i gigten når biologiske eller syntetisk targeterede lægemidler stoppes abrupt eller dosis nedtrappes sammenlignet med forsættelse af

standard dosis. Ingen randomiserede studier med en psoriasisgigt studiepopulation blev identificeret. Metaanalyserne viste en særdeles forøget risiko for både opblussen i gigten samt vedvarende opblussen i gigten, når biologisk behandling blev stoppet abrupt sammenlignet med fortsættelse af standard dosis. Dosisnedtrapning af biologiske eller syntetisk targeterede lægemidler versus fortsættelse af standard dosis medførte en signifikant øget risiko for opblussen i gigten men ikke for vedvarende opblussen i gigten. Derudover viste en netværksmetaanalyse en særdeles forøget risiko for både opblussen i gigten og vedvarende opblussen i gigten når abrupt ophør blev sammenlignet med dosisnedtrapning.

Studie II er et 18-måneder langt pragmatisk, randomiseret, ikke blindet, ækvivalensstudie. Studiets formål var at undersøge, om algoritmebaseret dosisnedtrapning af biologisk medicin guidet efter sygdomsaktivitet sammenlignet med fortsættelse af den biologiske medicin efter vanlig praksis medførte en signifikant dosisreduktion samtidig med at ro i gigten fastholdes. Et-hundrede-og-to-og-fyrre patienter med leddegigt, psoriasisgigt eller rygsøjlegigt med langvarig ro i gigten på stabil dosis biologisk medicin gennem ≥12 måneder blev inkluderet og randomiseret i studiet. I nedrapningsgruppen blev dosisintervallet af den biologiske medicin forlænget efter en algoritme guidet af sygdomsaktiviteten til opblussen i gigten eller total ophør med den biologiske medicin. Kontrolgruppen fortsatte uændret med deres biologiske behandling, dog var en mindre øgning i dosisintervallet tilladt hvis patienten ønskede dette. Ækvivalent sygdomsaktivitet mellem studiet to grupper blev påvist ved 18-måneders opfølgningen til trods for at signifikant flere patienter i nedtrapningsgruppen havde reduceret deres biologiske behandling med ≥50%. Resultaterne fra dettes studie kan bruges til at kvalificere dosisnedtrapning af biologisk medicin mellem patient og læge i almindelig, klinisk praksis.

Studie III havde til formål at undersøge, om potentielle prædiktive faktorer for succesfuld dosisnedtrapning af biologisk medicin kunne identificeres ud fra baseline karakteristika baseret på data fra studie II (BIODOPT-studiet). En tredjedel af patienterne i nedtrapningsgruppen opnåede succesfuld dosisnedtrapning af deres biologiske behandling ved 18-måneders opfølgningen. En multivariabel regressionsanalyse identificerede bedre mental helbred ved studiets start som en potentiel vigtig prædiktor. Studies resultater skal dog tolkes med forsigtighed, da fremtidige studier er nødvendige for at opnå yderlig indsigt i prædiktorer hos patienter med kroniske, inflammatoriske gigtsygdomme. Baseret på dette studie synes Short Form 36 (SF-36) dog at bidrage med yderlig indsigt til klinikeren og patienten når muligheden for dosisnedtrapning drøftes.

Efter evaluering af mulige fordele og ulemper til dosisnedtrapning af biologisk medicin viste denne afhandling, at dosisnedtrapning bør foretrækkes over abrupt ophør hos patienter med kroniske, inflammatoriske gigtsygdomme med langvarig ro

i gigten. Algoritmebaseret dosisnedtrapning af biologisk medicin guidet efter sygdomsaktivitet medførte at signifikant flere patienter i nedtrapningsgruppen reducerede deres biologiske behandling med ≥50% samtidig med at sygdomsaktiviteten forblev ækvivalent mellem studiets to grupper. Bedre mentalt helbred ved studiets start var den eneste potentielt vigtige prædiktor for succesfuld dosisnedtrapning af biologisk medicin.

ACKNOWLEDGEMENTS

PREFACE

This PhD thesis provides an extended summary of research carried out between 2018 and 2022 in collaboration between the Department of Rheumatology at Aalborg University Hospital, the Section for Biostatistics and Evidence-Based Research at the Parker Institute at Bispebjerg and Frederiksberg Hospital, the Department of Rheumatology at Aarhus University Hospital, the Department of Rheumatology at Odense University Hospital, and the Department of Rheumatology at Silkeborg Regional Hospital. The research was investigator-initiated, no funding parties were involved in planning or conducting the studies nor analysing or publishing study data.

The overall purpose of this dissertation was to evaluate if patients with IA treated with biological therapies and in sustained remission or LDA can reduce dose of their treatment and maintain stable disease activity.

The PhD thesis consist of five chapters: Chapter 1 provide a broad overview into the research area, Chapter 2 describe the aim of this dissertation, Chapter 3 provide an overview of the included studies, Chapter 4 contain a summarising discussion and Chapter 5 sum up the conclusion of this PhD thesis together with perspectives for future research.

LIST OF PAPERS

This thesis is based on the following four papers which are presented in full length with supplementary files as Appendix A-D. Throughout the thesis, the papers are referred to as:

Paper I (Study I)
Uhrenholt L, Christensen R, Dinesen WKH, Liboriussen CH, Andersen SS, Dreyer L, Schlemmer A, Hauge EM, Skrubbeltrang C, Taylor PC, Kristensen S. Risk of flare after tapering or withdrawal of b-/tsDMARDs in patients with RA or axSpA: A systematic review and meta-analysis. *Rheumatology (Oxford) 2021; keab902.*

Paper II (Study II)
Uhrenholt L, Schlemmer A, Hauge EM, Christensen R, Dreyer L, Suarez-Almazor ME, Kristensen S. Dosage reduction and discontinuation of biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: protocol for a pragmatic, randomised controlled trial (the BIOlogical Dose OPTimisation (BIODOPT) trial). *BMJ Open 2019;9:e028517.*

Paper III (Study II)
Uhrenholt L, Christensen R, Dreyer L, Hauge EM, Schlemmer A, Loft AG, Rasch MNB, Horn HC, Gade KG, Østgård RD, Taylor PC, Duch K, Kristensen S. Disease activity-guided tapering of biologics in patients with inflammatory arthritis: A pragmatic, randomised, open-label, equivalence trial. (Submitted).

Paper IV (Study III)
Uhrenholt L, Duch K, Christensen R, Dreyer L, Hauge EM, Schlemmer A, Taylor PC, Kristensen S. Predicting successful tapering in patients with inflammatory arthritis tapering biologics: Secondary analyses based on the BIODOPT trial. (To be submitted).

ABBREVIATIONS

IA: Inflammatory arthritis

RA: Rheumatoid arthritis

PsA: Psoriatic arthritis

axSpA: Axial spondyloarthritis

ARA: American Rheumatism

ACR: American College of Rheumatology

EULAR: European Alliance of Associations for Rheumatology

CASPAR: Classification criteria for psoriatic arthritis

ASAS: Assessment of SpondyloArthritis International Society

AS: Ankylosing spondylitis

SI: Sacroiliac

T2T: Treat-to-target

LDA: Low disease activity

bDMARD: Biological disease-modifying antirheumatic drug

tsDMARDs: Targeted synthetic disease-modifying antirheumatic drugs

JAKi: Janus kinase inhibitor

PROMs: Patient-reported Outcome Measures

DAS28-CRP: Disease Activity Score28-CRP

ESR: Erythrocyte Sedimentation Rate

ASDAS: Ankylosing Spondylitis Disease Activity Score

BASMI: Bath Ankylosing Spondylitis Disease Activity Index

DAPSA: Disease Activity in Psoriatic Arthritis

OMERACT: Outcome Measures in Rheumatology

RCTs: Randomised controlled trials

TNFis: Tumor necrosis factor inhibitors

MTX: Methotrexate

95% CI: 95% confidence interval

SLR: Systematic literature review

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis

REML: Restricted maximum likelihood

RR: Risk ratio

POR: Peto's Odds Ratio

IL6i: Interleukin-6 inhibitor

OR: Odds ratio

GCP: Good Clinical Practice

RD: Risk difference

CONSORT: Consolidated Standards of Reporting Trials

ITT: Intention-to-treat

VAS: Visual Analogue Scale

MRI: Magnetic resonance imaging

AUC: Area under the receiving operator characteristic curve

HAQ-DI: Health Assessment Questionnaire Disability Index

SF-36: Short Form Health Survey 36

PCS: Physical Component Summary

MCS: Mental Component Summary

TRIPOD: Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

MDA: Minimal disease activity

csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs

ADAb: Anti-drug antibodies

AEs: Adverse events

SAEs: Serious adverse events

NSAIDs: Non-steroidal anti-inflammatory drugs

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Table 1.2. Essential proinflammatory cytokines in inflammatory arthritis.

Table 1.3. Mode of actions for biological and targeted synthetic disease-modifying antirheumatic drugs used to treat patients with inflammatory arthritis when this PhD study was initiated.

Table 1.4. Patient-reported outcome measures most often evaluated in patients with inflammatory arthritis in clinical practise and clinical trials.

Table 1.5. Clinical measures evaluated by the physician in the BIODOPT trial (Study II of this thesis) and often evaluated in clinical practise and clinical trials.

Table 1.6. Composite scores used to evaluate disease activity in patients with inflammatory arthritis in Denmark.

Table 1.7. Studies evaluating tapering of biologics in patients with inflammatory arthritis.

Table 1.8A. Studies evaluating withdrawal of biologics in patients with rheumatoid arthritis.

Table 1.8B. Studies evaluating tapering of biologics in patients with rheumatoid arthritis.

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CHAPTER 1. BACKGROUND

1.1. INFLAMMATORY ARTHRITIS

Inflammatory arthritis (IA) is a term used to describe a group of chronic, autoimmune, inflammatory joint diseases with a heterogenous presentation as symptoms include peripheral and/or axial inflammation accompanied by extra-articular manifestations. In the rheumatology outpatient clinic, rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) are among the three most common IA diseases. Throughout this thesis, IA includes the diagnoses RA, PsA and axSpA.

Diagnosing IA can be challenging, as some symptoms overlap; moreover, no single clinical, laboratory or radiologic feature can be used as a "gold standard" to make a define diagnosis (1). Specific classification criteria have been developed:

- *RA:*
  - American Rheumatism Association (ARA) 1987 criteria (2)
  - American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010 criteria (3)
- *PsA:*
  - Moll and Wright 1973 criteria (4)
  - 2006 Classification criteria for psoriatic arthritis (CASPAR) (5)
- *AxSpA:*
  - Assessment of SpondyloArthritis International Society (ASAS) 2009 classification criteria (6)
  - Modified New York ankylosing spondylitis (AS) 1984 criteria (7)

An overview of IA disease characteristics is presented in Table 1.1.

Table 1.1. Disease characteristics of inflammatory arthritis.

Variable	RA	PsA	AxSpA
Joint involvement	Peripheral, symmetric polyarthritis[1], often: MCP, PIP, MTP, wrist and ankle (17)	Peripheral arthritis: asymmetric olgoarthritis[2] or symmetric polyarthritis, often DIP (12) Axial spondyloarthritis: 50% (12) Enthesitis: 30-50% (12) Dactylitis: 40-50% (12)	Axial spondyloarthritis Peripheral asymmetric oligoarthritis, often: ankles, hips, knees, shoulders and sternoclaviculars (8) Enthesitis (9) Rarely dactylitis (9)
Extra-articular manifestations	Rheumatoid nodules, pericarditis, pleuritis, pulmonal involvement and vasculitis (18)	Skin psoriasis, nail psoriasis, less frequent uveitis, and IBD (12,13).	Uveitis, skin/nail psoriasis, and IBD (9)
Prevalence	0.5-1.0% (18)	0.22% (14); however, could be higher as 20% of PsO (prevalence 2-3% (12)) have PsA (15).	0.3-1.4% (9)
Gender distribution[3]	2:1 (17)	1:1 (12)	Nr-axSpA: 1:1, AS: 3:1 (9,10)
Age at disease onset	40 to 70 years of age (17)	30 to 50 years of age (16)	20 to 30 years of age (11)

RA: *rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, MCP: Metacarpophalangeal, PIP: Proximal interphalangeal, MTP: Metatarsophalangeal, DIP: Distal interphalangeal, IBD: Inflammatory bowel disease, PsO: psoriasis, nr-axSpA: Non-radiographic axial spondyloarthritis, AS: Ankylosing spondylitis.* [1]*: >5 joints,* [2]*: ≤4 joints,* [3]*: Women: Men.*

1.2. PATHOGENESIS

The pathogenesis of IA is complex and not understood in full detail. However, the disease is driven by uncontrolled activation of T cells and/or B cells; thereby, initiating several proinflammatory cascades, leading to production of cytokines and resulting in inflammation (19). Essential proinflammatory cytokines are presented in Table 1.2. Proinflammatory cytokines facilitate synovial inflammation with formation of pannus and activation of osteoclasts; thereby, risking cartilage and bone damage with bone erosions (12,19–21). Furthermore, in patients with axial disease, proinflammatory cytokines facilitate inflammation in the interface between cartilage and bone in the spine and the sacroiliac (SI) joints resulting in osteoproliferation and possible formation of syndesmophytes and ankylosis (9,19). Similarly, inflammation at the entheseal site can result in enthesophyte growth (12,22).

Table 1.2. Essential proinflammatory cytokines in inflammatory arthritis.

Cytokine	RA	PsA	AxSpA
TNF-α	X	X	X
IL-1	X		
IL-6	X		
IL-12		X	X
IL-17A	X	X	X
IL-23		X	X

RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, TNF-α: tumor necrosis factor alpha, IL: interleukin.

1.3. TREATMENT OF INFLAMMATORY ARTHRITIS

Treatment of musculoskeletal manifestations of IA are recommended to be managed in rheumatology outpatient clinics based on shared decision-making with the patient (23–25). Treatment should be initiated as soon as possible (23–25) with consideration to both joint involvement and extra-articular manifestations. Bridging therapy with short-term oral, intraarticular or intramuscular glucocorticoids is often used (23,24).

In RA and PsA, a disease activity-guided treat-to-target (T2T) approach with treatment changes approximately every 3 months are advised if the target of remission or low disease activity (LDA) not is reached (23,24). In axSpA, recommendations for and against T2T exist due to lack of direct evidence (25,26).

If first-line therapy is insufficient to reach the treatment target, it is recommended to consider intensifying the treatment with a biological agent (23–25).

1.3.1. BIOLOGICAL AND TARGETED THERAPIES

Biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs, respectively) are drugs that target specific parts of the immune system; thereby, blocking proinflammatory cascades. In 1998, the first biological agent for treatment of IA was approved (27) and since various therapies with different modes of actions have been developed. Modes of action include (Table 1.3) (28):

- **Anti-cytokine therapies:** binds to a target cytokine in the extracellular space or to the receptor (of the target cytokine) on the cell surface; thereby, inhibiting the binding between the target cytokine and the cell receptor; thus, blocking cell activation (29).
- **B-cell depletion:** binds to CD20 on the B-cells; thereby, inducing cytotoxicity and B-cell apoptosis. Thus, B-cells are depleted which result in e.g. decreased proinflammatory cytokines and antibody production (30).
- **Co-stimulation blockers:** binds to CD80/CD86 on the antigen-presenting cell; thereby, preventing binding between the antigen-presenting cell and the T-cell. Thus, the T-cell cannot be activated (30).
- **Janus kinase inhibitors (JAKi):** blocks phosphorylation at the intracellular part of the cell receptor; thereby, blocking activation of the JAK enzymes. Thus, the cell receptor (and thereby the cell) cannot be activated by extracellular cytokines (29).

The introduction of b- and tsDMARDs in the management of IA have resulted in better disease control as more patients reach an acceptable disease state such as remission or LDA (28,31,32). If first-line biologics are insufficient and the diagnosis is define, switch to another b- or tsDMARD is recommended (23–25).

Table 1.3. Mode of actions for biological and targeted synthetic disease-modifying antirheumatic drugs used to treat patients with inflammatory arthritis when this PhD study was initiated.

Cytokine	Anti-cytokine therapy	B-cell depletion	Co-stimulation blockers	JAK inhibition
Abatacept			X	
Adalimumab	X[1]			
Baricitinib				X
Certolizumab pegol	X[1]			
Etanercept	X[1]			
Golimumab	X[1]			
Infliximab	X[1]			
Ixekizumab	X[2]			
Rituximab		X		
Secukinumab	X[2]			
Sarilumab	X[3]			
Tocilizumab	X[3]			
Tofacitinib				X
Ustekinumab	X[4]			

JAK: janus kinase. [1]: target tumor necrosis factor alpha, [2]: target interleukin 17A, [3]: target interleukin 6, [4]: target interleukin 12/23.

1.4. MONITORING DISEASE ACTIVITY

Evaluation of disease activity in patients with IA include the patient's assessment of various patient-reported outcomes and the physician's evaluation of various clinical measures. Table 1.4 provides an overview of essential patient-reported outcome measures (PROMs) and Table 1.5 of essential clinical measures used in the management of IA.

Table 1.4. Patient-reported outcome measures most often evaluated in patients with inflammatory arthritis in clinical practise and clinical trials.

PROMs	Range	Aims to assess	Validation/ Evaluation
HAQ-DI	0-3	Physical function based on eight aspects. High score equal low physical function.	RA (33,34) PsA (35), AxSpA (36)
Pain VAS	0-100	Pain intensity on a 100 mm VAS scale. High score equal high pain level.	RA (34), PsA (37), AxSpA (38)
Fatigue VAS	0-100	Fatigue severity intensity on a 100 mm VAS scale. High score equal high fatigue level.	RA (34), PsA (37), AxSpA (39)
Patient Global Health VAS	0-100	Impact of arthritis disease activity on global health on a 100 mm VAS scale. High score equal high impact on global health.	RA (40), PsA (41), AxSpA (39)
BASDAI	0-100	Disease activity in axSpA based on six questions answered on a 100 mm VAS scale. High score equal high disease activity.	AxSpA (39,42)
SF-36 PCS	0-100	Physical function based on aggregating scores from the eight SF-36 subscales. High score equal high physical function.	RA (43), PsA (44), AxSpA (39)
SF-36 MCS	0-100	Mental function based on aggregating scores from the eight SF-36 subscales. High score equal high mental function.	RA (43), PsA (44), AxSpA (39)

PROMs: patient-reported outcome measures, HAQ-DI: Health Assessment Questionnaire Disability Index, RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, VAS: Visual Analog Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, SF-36: Short-form 36, PCS: Physical component summary, MCS: Mental component summary.

Table 1.5. Clinical measures evaluated by the physician in the BIODOPT trial (Study II of this thesis) and often evaluated in clinical practise and clinical trials.

Clinical measure	Range	Aim to assess	Validation/ Evaluation
Tender joint count	0-68[1]	Joint tenderness of 68 joints by joint movement or by applying sufficient pressure[2]. High score equal high tender joint count.	RA (45), PsA (46), AxSpA (47)
Swollen joint count	0-66[1]	Joint swelling of 66 joints assessed by palpation (soft tissue swelling or fluctuation). High score equal high swollen joint count.	RA (45), PsA (46), AxSpA (47)
SPARCC	0-16	Entheseal tenderness of 16 sites assessed by palpation. High score equal high tender enthesis count.	PsA (48), AxSpA (49)
Dactylitis count	0-20	Swelling of an entire digit from the base to the tip assessed by affected fingers and toes. High score equal high dactylitis count.	PsA (50), AxSpA (51)
PASI	0-72	Psoriasis skin involvement assessed by erythema, induration, scaling, and body surface area. High score equal severe skin psoriasis.	PsA (50), AxSpA (52)
mNAPSI	0-130	Psoriasis nail involvement assessed by 8 features on each fingernail. High scores equal severe nail psoriasis.	PsA (53), AxSpA (52)
BASMI	0-100	Spinal mobility assessed by cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's, and intermalleolar distance. High score equal low spinal mobility.	AxSpA (54)
CRP	0-900 mg/L	Inflammation level measured by blood C-Reactive Protein level. High score equal high inflammation.	Generic (55)

RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, SPARCC: Spondyloarthritis Research Consortium Canada, PASI: Psoriasis Area Severity Index, mNAPSI: Modified Nail Psoriasis Severity Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, CRP: C-Reactive Protein, mg: milligram, L: litre. [1]: A shorter version (0-28) with focus on upper extremities is available. [2]: Sufficient pressure on the joint is applied when whitening of the examiner's nail bed used to palpate the joint is seen.

PROMs and clinical measures are combined in composite scores to give the physician a translatable estimate of disease activity. Several disease activity scores exist for IA; however, Disease Activity Score 28 C-Reactive Protein (DAS28-CRP) (56) is one of the most frequently used scores to monitor patients with RA and is endorsed in Denmark. As presented in Table 1.6, the score combines patient global health VAS, tender and swollen joint count (out of 28) performed by a physician, and CRP. Cut-off values that divides DAS28-CRP into categories reflecting different levels of disease activity has been defined (57); however, the cut-offs were based on the original DAS28 using erythrocyte sedimentation rate (ESR) instead of CRP. Thus, it has been debated if the cut-off values for DAS28-CRP should be modified (58–61) but as the ESR-based categories is endorsed in Denmark, they were also used in this PhD study.

Ankylosing Spondylitis Disease Activity Score (ASDAS) (62,63) is frequently used to monitor patients with axSpA and is also recommended in the management of patients with axSpA in Denmark and endorsed by ASAS and EULAR (25). ASDAS combines the patients assessment of global health VAS, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) question 2, question 3, and question 5, and CRP. The score is also divided into categories reflecting different levels of disease activity; however, as presented in Table 1.6, a moderate disease activity state is not defined as the range goes directly from LDA to high disease activity (64).

Several composite scores are used worldwide to monitor patients with PsA; no international consensus exist on which score is the most optimal or preferred tool (24,65,66). However, DAS28-CRP has for long been used to monitor patients with PsA in Denmark but recently the Disease Activity index for PSoriatic Arthritis (DAPSA) score (67) also became an endorsed tool. DAPSA combines the patient pain VAS and global health VAS, tender and swollen joint count (out of 66/68) performed by a physician, and CRP. Cut-off values that divides score into categories reflecting different levels of disease activity has been defined (68).

Table 1.6. Composite scores used to evaluate disease activity in patients with inflammatory arthritis in Denmark.

Score	Components	Range	Disease activity
DAS28-CRP (56)	Patient Global Health VAS (0-100) Tender joint count (0-28) Swollen joint count (0-28) CRP (mg/L)	0-9.4	High: >5.1 Moderate: 3.3-5.1 Low: 2.6-3.2 Remission: <2.6 (57)
ASDAS (62)	Patient global health VAS (0-10[1]) Backpain[2] (0-10[1]) Peripheral pain/swelling[3] (0-10[1]) Morning stiffness[4] (0-10[1]) CRP (mg/L)	0.6-∞	Very High: >3.5 High: 2.1-3.5 Low: 1.3-2.0 Remission: <1.3 (64)
DAPSA (67)	Patient pain VAS (0-10[1]) Patient Global Health VAS (0-10[1]) Tender joint count (0-68) Swollen joint count (0-66) CRP (mg/dl)	0~200	High: >28 Moderate: 15-28 Low: 5-14 Remission: 0-4 (68)

DAS28-CRP: Disease Activity Score28-C-Reactive Protein, VAS: Visual Analog Scale, CRP: C-reactive protein, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, dl: decilitre. [1]: Assessed on a VAS scale from 0-10 cm, [2]: BASDAI question 2, [3]: BASDAI question 3, [4]: BASDAI question 5.

1.4.1. ARTHRITIS FLARE

Patients with IA in sustained LDA can experience a worsening in disease activity for no apparent reason or as a result of e.g. an infection, pause in therapy due to surgery, or dose alterations due to e.g. tapering. Arthritis flare is a term used to describe a worsening in disease activity of sufficient intensity and duration to make the physician consider if a change in arthritis treatment is needed (69). However, up until recently no validated criteria for flare existed; therefore, flare was evaluated on the physician's discretion which allows for possible heterogeneity in the interpretation. In 2013, the Outcome Measures in Rheumatology (OMERACT) organisation validated and recommended the use of a DAS28-based flare criteria for patients with RA (70); a flare was defined as: ΔDAS28 >1.2 or ΔDAS28 >0.6 AND a current DAS28 ≥3.2. ASAS endorsed and validated an ASDAS-based criteria for flare in 2018 for patients with axSpA (71); a flare was defined as: ΔASDAS ≥0.9. No flare criteria exist for PsA; a result of the lack of international consensus on which composite score is preferable for the management of PsA. Therefore, a

pragmatic approach is to use the DAS28-based flare criteria in patients with peripheral involvement and the ASDAS-based flare criteria in patients with axial involvement.

1.5. DOSE REDUCTION OF BIOLOGICAL THERAPIES

The rationale for dose reduction of b- or tsDMARDs in patients with IA in sustained LDA are to manage the arthritis disease activity with the lowest possible drug dose or the longest dosing interval possible.

A potential advantage to dose reduction for the individual patient could be a lower risk of adverse drug reactions. Furthermore, if the dosing interval is successfully prolonged or the drug successfully withdrawn, a result would be fewer necessary visits to the outpatient clinic to receive b-/tsDMARD treatment which could lower the individual patient's disease burden. From a societal perspective, previous research have demonstrated a significant cost saving after dose reduction of biologics among patients with IA (72–74); although the cost savings might be less extensive as more biosimilars have emerged.

Potential disadvantages to dose reduction must also be taken into consideration of which the most feared is persistent flare that cannot be managed by dose escalation to standard dose and therefore require switch to another biological therapy.

1.5.1. DOSE REDUCTION STRATEGIES

Different strategies for dose reduction include:

- *Withdrawal:* abrupt discontinuation without prior dose reduction i.e. from standard dose (100%) to nothing (0%) in one step.
- *Fixed dose reduction:* one step tapering to a pre-specified, fixed dose or dosing interval e.g. from standard dose (100%) to 50% reduced dose or 50% increased dosing interval in one step.
- *Disease activity-guided tapering:* dose reduction after a pre-specified algorithm e.g. 25% dose reduction or 25% increased dosing interval every 3 month as long as disease activity is judged to be acceptable e.g. LDA.

Withdrawal is the most aggressive dose reduction strategy. As disease activity-guided tapering is continued until flare or complete drug withdrawal, the strategy is generally considered more aggressive than the fixed dose reduction strategy. However, as the disease activity-guided strategy allows the maximal tapering

possible it could be the most favourable strategy if flares easily are managed with dose escalation.

1.5.2. TREATMENT GUIDELINES

International treatment guidelines on the management of IA recommend to consider slowly tapering biologics if the patient is in sustained remission (23–25). The optimal duration of remission before tapering should be considered is not known; however, at least 6 months is generally recommended (24,25). Complete drug withdrawal is generally not recommended as it leads to flare in a significant proportion of patients (23–25).

Shared-decision-making between the patient and physician is highlighted as a pivotal part of tapering (24,25) and aspects important to the patient must be addressed e.g. fear of arthritis flare resulting in physical disability and difficulty with caring for their job.

EULAR recommend a gently tapering approach in patients with RA with joint damage due to a high risk of damage progression (23). The ASAS/EULAR treatment guideline for axSpA conclude that tapering by interval prolongation is the most practical approach (25).

1.5.3. EVALUATION OF THE EVIDENCE

This section provides an overview of the available evidence on biologic dose reduction before initiation of this PhD project; therefore, articles published after April 2018 are not included in this section but discussed later in the thesis. Furthermore, randomised controlled trials (RTCs) evaluating tapering and/or withdrawal to continuation of biologics is evaluated in Study I and therefore not included in this section. Thus, this section includes RCTs not available for inclusion in Study I as well as prospective observational studies as these study designs generally have the highest quality of evidence. Only studies with ≥24 weeks follow-up are included to provide a more reliable picture of dose reduction including data on long-term effects such as the risk of flare and persistent flare.

As presented in Table 1.7 to 2.0 and in Study I, dose reduction is more frequently evaluated for tumour necrosis factor inhibitors (TNFis) among patients with IA than for therapies with other modes of actions e.g. B-cell depletion or co-stimulation blockers. No studies on tsDMARD dose reduction published before May 2018 were identified. Furthermore, biologic dose reduction is more often assessed in patients with RA than in patients with PsA or axSpA; a large number of RCTs are conducted

in patients with RA whereas only a few RCTs are performed in patients with axSpA and none in patients with PsA. Thus, the overall quality of the available evidence varies due to differences in number of conducted trials as well as differences in study design. Moreover, the studies often only assess one drug per trial; thus, evidence on head-to-head comparisons of tapering and/or withdrawal of different biologics in the same study is sparse. A Cochrane review from 2014, which evaluate dose reduction of TNFi in patients with RA, recommended due to lack of evidence that future research also should focus on non-TNFi as well as other inflammatory arthritis diagnosis than RA e.g. PsA and/or axSpA (75).

The duration of acceptable disease activity state before dose reduction is initiated varies between studies as presented in Table 1.7 to 2.0 and in Study I; however, most studies require at least 6 months of remission or LDA. Moreover, heterogeneity exist in the criteria for disease activity before dose reduction is initiated which could be explained by the lack of international consensus on the preferred composite scores for monitoring patients with PsA and previously for the management of patients with axSpA. The difference in flare criteria is a consequence of the lack in validated flare criteria as the DAS28-based flare criteria for RA first was developed in 2013 (70) and the ASDAS-based flare criteria for axSpA in 2018 (71).

A large proportion of the available RCTs are efficacy (superiority) studies sponsored by the manufacturer; thus, in part 1 treatment with a specific biologic is evaluated in patients with an insufficient initial treatment response. In part 2, patients reaching an acceptable disease state (remission or LDA) taper or withdraw their biological therapy. However, efficacy studies could be biased as the manufacturer have an economical interest in keeping more patients on standard dose which could be reflected in e.g. the chosen study design, primary outcome or analysis plan. Often, the more aggressive withdrawal strategy is used in these trials resulting in a higher flare risk. On the contrary, the study population in efficacy studies are often newly diagnosed patients who start first-line biological therapy. Thus, this could result in more patients maintaining an acceptable disease activity despite biologic tapering/withdrawal compared to studies with a study population of patients with more established disease and previous biologic failure history i.e. treated with biological therapy number ≥2.

Most RCTs evaluating dose reduction of biologics have a superiority design; thus, before initiation of this PhD study only three non-inferiority studies (76–78) and one equivalence study existed (79). The rationale against conducting a biologic dose reduction study as a superiority trial is discussed in detail in the next section. Two of the three non-inferiority trials evaluated a fixed dose reduction strategy (77,78) whereas one non-inferiority trial (76) and one equivalence trial (79) assessed disease activity-guided tapering. In the Cochrane review from 2013, disease activity-guided tapering using a treat-to-target approach is recommended over the fixed dose reduction strategy as the former was found more compatible with clinical practice

(75). Thus, the Cochrane Collaboration encourage future research to be directed towards disease activity-guided tapering of biologics.

Table 1.7. Studies evaluating tapering of biologics in patients with inflammatory arthritis.

First author Acronym Year	Study design (patients)	Disease activity before dose reduction	Strategy	Flare definition	Primary endpoint	Results
Cantini 2012 (80)	Case-control (cases: 53 PsA, controls: 17 RA)	PsA: fatigue VAS ≤10, pain VAS ≤10 OR BASDAI ≤4. No peripheral, axial or extra-articular disease. Normal CRP/ESR.. RA: DAS≤2.6 Duration not specified.	Adalimumab 40 mg/4W	Recurrence of articular or extra-articular disease	PsA: 28.9 ±8.4 months RA: 24.2 ±6.4 months	Remission: PsA 88.6% (47/53) and RA 17.6% (3/17). Time to flare: 8.3 ±3.4 months. All flaring patients regained remission after adalimumab dose escalation.
Murphy 2015 (74)	Observational (N: 79 IA[1])	DAS28 <2.6 or BASDAI <4 for ≥6 months	Adalimumab 40 mg/4W or etanercept 50 mg/EOW	Absence of remission	24 months	Remission: 56% (44/79). Cost-saving: 600,000 €/2 years

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| **Lesuis 2016** (81) | Observational (N: 232 IA[2]) | DAS28 <3.2 or BASDAI <4 or low disease activity judged by the rheumatologist. Duration not specified. | Individualised treatment advise | Not defined | October 2014 (study period started May 2014) | Stable disease activity despite more patients on reduced biologics (61% vs. previously 10%). 11 patients (5%) withdrew biologics. |

PsA: Psoriatic arthritis, RA: Rheumatoid arthritis, VAS: Visual Analog Scale, BASDAI: Bath Ankylosing Disease Activity Index, DAS: Disease Activity Score, mg: milligram, W: week, IA: Inflammatory arthritis, EOW: every other week. [1]: *45 patients with RA, 10 patients with PsA, and 24 patients with AS.* [2]: *153 patients with RA, 34 patients with PsA, and 40 patients with AS.*

Table 1.8A. Studies evaluating withdrawal of biologics in patients with rheumatoid arthritis.

First author Acronym Year	Study design (patients)	Disease activity at dose reduction	Strategy	Flare definition	Primary endpoint	Results
Brocq 2009 (82)	Observational (N: 21)	DAS28 <2.6 for ≥6 months, >5mg prednisolone per day, NSAID-free.	Adalimumab, etanercept, or infliximab withdrawal	DAS28 >3.2	12 months	Remission: 25% (5/20). Flare: 75% (15/20). Time to flare: 14.7 weeks. All regained LDA after TNFi re-treatment.
Tanaka RRR 2010 (83)	Observational (N: 114)	DAS28-ESR <3.2 for >24 weeks. Prednisone <5 mg/day.	Infliximab withdrawal	DAS28-ESR >3.2	12 months	LDA: 55% (56/102). Flare: 45% (46/102) Most patients regained LDA after infliximab re-treatment.
Van den Broek BEST 2011 (84)	Observational (N: 104)	DAS ≤2.4 for ≥6 months.	Infliximab withdrawal	DAS >2.4	Median: 7.2 years	Flare: 48% (50/104). 84% (42/50) regained DAS ≤2.4 after infliximab re-treatment.
Nishimoto DREAM 2014 (85)	Observational (N: 187)	DAS28-ESR <2.6 at ≥2 consecutive visits.	Tocilizumab withdrawal	DAS28 >3.2 at 2 visits or need rescue therapy	12 months	Flare: 87% (161/185) LDA: 13% (24/185)

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Takeuchi **2015** (86)	Observational (WG 34, CG 17)	DAS28-CRP <2.3. Duration not specified.	Abatacept withdrawal or continuation	DAS28 >2.7 at 2 visits or physician judged flare.	12 months	WG: Abatacept-free: 64.7% (22/34), flare: 26.5% (9/34). Time to flare: 149.6 ±34.5 days. DAS28: WG 2.9 and CG 2.0.
Tanaka **HONOR** **2015** (87)	Observational (WG 52, CG 23)	DAS28-ESR <2.6 for 6 months, steroid-free and NSAID-free	Adalimumab withdrawal or continuation	DAS28-ESR ≥ 3.2	12 months	Remission: WG 48% (25/52), CG 83% (19/23). Flare: WG 40%. All LDA after adalimumab re-treatment.

N: Number of patients, DAS28: Disease Activity Score28, NSAID: Non-steroidal anti-inflammatory drugs, LDA: low disease activity, TNFi: Tumor necrosis factor inhibitor, ESR: Erythrocyte Sedimentation Rate, WG: withdrawal group, CG: Control group, CRP: C-reactive protein.

Table 1.8B. Studies evaluating tapering of biologics in patients with rheumatoid arthritis.

First author Acronym Year	Study design (patients)	Disease activity at dose reduction	Strategy	Flare definition	Primary endpoint	Results
Van der Maas 2012 (88)	Observational (N: 51)	DAS28 <3.2 for ≥6 months	Infliximab dose taper by 25% every 8-12 week	ΔDAS28 ≥1.2 at two visits OR ΔDAS28 ≥0.6 +current DAS28 >3.2.	12 months	Withdraw: 16% (8/51). Taper: 45% (23/51). Infliximab dose: 224 mg to 130 mg. DAS28: 2.5 to 2.8. Cost-saving: 3,474€/patient.
Emery PRIZE 2014 (89)	RCT (TG: 63, WG: 65, PG: 65)	DAS28 ≤3.2 at week 39 and <2.6 at week 52 in period 1.	MTX + etanercept dose taper by 50%, MTX + etanercept withdrawal, or placebo	DAS28 >3.2	39 weeks	Remission: TG 79% (50/63), WG 54% (35/65), PG 38% (25/65). ΔDAS28: TG 0.3, WG 1.0, PG 2.0. Flare: TG: 8% (5/63), WG: 28% (18/65), PG: 45% (29/65).
Kikuchi 2017 (90)	Observational (N: 25)	DAS28-ESR ≤2.6 for ≥3 months	Tocilizumab interval prolongation to 8 mg/kg/6 weeks	DAS28 >3.2 at two consecutive visits.	54 weeks	Remission: 87.5% (21/24). DAS28: 0.95 (baseline) and 1.77 (week 54).

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| **Yasuda MATADOR 2017** (91) | Observational (N: 53) | DAS28 <2.7 for ≥6 months | Abatacept dose taper to 250 mg/body/month | Not defined | 48 weeks | Remission: 77% (41/53). Flare: 9% (5/53). All regained remission after abatacept dose escalation. |

N: Number of patients, DAS28: Disease Activity Score28, mg: milligram, RCT: randomised controlled trial, TG: tapering group, WG: withdrawal group, PG: placebo group, MTX: methotrexate, Δ: change, ESR: Erythrocyte Sedimentation Rate, kg: kilogram.

Table 1.9A. Studies evaluating withdrawal of biologics in patients with axial spondyloarthritis.

First author Acronym Year	Study design (patients)	Disease activity at dose reduction	Strategy	Flare definition	Primary endpoint	Results
Baraliakos 2007 (92)	Observational (N: 42 AS)	BASDAI 2.5 at baseline. Duration not specified.	Infliximab withdrawal	BASDAI and physician global health ≥ 4	48 weeks	Flare: 97.6% (40/41). Time to flare: 17.5 weeks. One patient successfully withdrew infliximab. All flaring patients regained LDA after infliximab re-treatment.
Song ESTHER 2012 (93)	Observational (after RCT) (N: 17 axSpA: etanercept = 13, SSZ = 4)	ASAS remission + MRI remission[1] at week 48 of period 1	Etanercept or SSZ withdrawal	ΔBASDAI >2 compared to week 48 in period 1	48 weeks (period 2)	Flare: etanercept 69% (9/13) and SSZ 75% (3/4). Time to flare: etanercept 24.4 weeks, SLZ 39.6 weeks. All flaring patients regained remission after re-treatment. 23.5% (4/17) successfully withdrew etanercept.

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| **Haibel 2013** (94) | Observational (N: 24 axSpA) | ASAS40 response at the end of year 1 (of period 1). Duration not specified. | Adalimumab withdrawal | Loss of ASAS40 response | 2 years (period 2) | Flare year 1 (period 2): 79% (19/24). Time to flare: 14.7 weeks ±5.5 weeks. At year 1 (period 2) 63.2% (12/19) regained ASAS40 after adalimumab re-treatment and 73.7% (15/19) at year 2. |

N: Number of patients, AS: ankylosing spondylitis, BASDAI: Bath Ankylosing Disease Activity Index, LDA: low disease activity, RCT: randomised controlled trial, axSpA: axial spondyloarthritis, SSZ: sulfasalazine, ASAS: Assessment of SpondyloArthritis International Society, MRI: Magnetic resonance imaging, Δ: change. [1]: MRI remission: no active inflammation in the spine and sacroiliac joints on whole-body MRI.

Table 1.9B. Studies evaluating tapering of biologics in patients with axial spondyloarthritis

First author Acronym Year	Study design (patients)	Disease activity at dose reduction	Strategy	Flare definition	Primary endpoint	Results
Mörck 2013 (95)	Observational (N: 18 AS)	Mean BASDAI 2.1 at week 52 in period 1.	Infliximab 3 mg/kg/8W	Not defined	12 months	Stable BASDAI despite lower infliximab dose. Two patients discontinued study due to lack of efficacy.
Almirall 2015 (96)	Observational (N: 42 axSpA)	BASDAI ≤2, no arthritis/enthesitis, normal CRP ≥6 months.	Etanercept 50mg/ 10D or 25 mg/W, infliximab 3 mg/kg/ 8W, adalimumab 40 mg/3W	BASDAI ≥4 independent of arthritis or CRP increase	12 months	LDA: 76.2% (32/42) Flare: 23.8% 10/42)
Arends 2015 (97)	Observational (N: 58 AS)	BASDAI <4 for ≥6 months	Disease activity-guided tapering to approximately 50% interval prolongation	Not defined	24 months	Reduced dose. 53% (31/58). Flare: 47% (27/58). Almost all flaring patients regained disease activity state after TNFi re-treatment.

Continues on the next page.

Závada 2016 (98)	Observational (N: 136 AS: TG 53, CG 83)	BASDAI<4 for >6 months	Tapering adalimumab, etanercept or infliximab after the physicians discretion	BASDAI >4 or ΔBASDAI ≥1.5	12 months	TG received median 67% of standard dose. Flare: TG 22.6% (12/53) and CG 15.7% (13/83). Disease activity was similar. Cost savings: 4214€/year.

N: Number of patients, AS: ankylosing spondylitis, BASDAI: Bath Ankylosing Disease Activity Index, mg: milligram, kg: kilogram, W: week, axSpA: axial spondyloarthritis, CRP: C-reactive protein, D: day, LDA: low disease activity, TNFi: Tumor necrosis factor inhibitor, TG: tapering group, CG: Control group.

Table 2.0. Studies evaluating tapering or withdrawal of biologics in patients with psoriatic arthritis.

First author Acronym Year	Study design (patients)	Disease activity at dose reduction	Strategy	Flare definition	Primary endpoint	Results
Araujo 2015 (99)	Observational (N: 26)	Absence of arthritis, dactylitis, enthesitis or axial disease + PASI<1 for ≥6 months.	TNFi and/or MTX withdrawal	Judged by the physician	6 months	Flare: TNFi 83.3% (10/12) and MTX 71.4% (10/14). Time to flare: 74.5 days ±51.7 days.
De Stefano 2018 (100)	Observational (N: 29)	Remission[1] at week 12 and 16	Etanercept 25 mg/W, possibly 25 mg/EOW if remission at week 24 + 28.	Recurrence of articular, extra-articular disease or increased CRP/ESR	48 weeks	Remission: 93% (27/29) of which 15 (51%) received etanercept 25mg/EOW, 6 (21%) etanercept 25 mg/W and 6 (21%) etanercept 25 mg/bW

N: Number of patients, PASI: Psoriasis Area Severity Index, TNFi: Tumor necrosis factor inhibitor, MTX: methotrexate, mg: milligram, W: week, EOW: every other week, CRP: C-reactive protein, ESR: Erythrocyte Sedimentation Rate, bW: biweekly. [1]: ASAS partial remission, absence of arthritis, enthesitis, dactylitis and extra-articular disease, normal CRP and no additional intake of NSAIDs or glucocorticoids.

1.6. PREDICTING SUCCESSFUL TAPERING

Predictive factors are patient or disease characteristics that can be used to predict a patient's response to a specific intervention (101). Information from multiple independent variables can be combined in regression analyses to provide risk estimates for qualifying the discussion between the physician and the patient when considering the risk of the intervention. Thus, identifying potential predictive factors for successful tapering of biologics in patients with IA would help to distinguee between low-risk patients likely to achieve successful tapering and high-risk patients likely to experience a significant arthritis flare.

In a systematic literature review by Tweenhuysen et al., only adalimumab serum trough level was identified as a potential predictor of successful biologic tapering among patients with RA (102). However, the results were only based on two studies of which one study have been disputed; therefore, certainty of the evidence was labelled as 'limited'. Thus, no consistent predictors for successful biologic tapering in patients with IA have yet been identified but researchers are encouraged by the Cochrane Collaboration to attempt to identify possible predictive factors to qualify the discussion on who to taper (103).

1.7. RANDOMISED CONTROLLED TRIAL DESIGNS

1.7.1. RATIONALE OF DIFFERENT RCT DESIGNS

RCTs are generally accepted as the "gold standard" for comparing the effect of therapeutic interventions (104). Superiority trials are designed to assess if treatment A is better than placebo (or treatment B) by demonstrating a significant efficacy difference between the interventions in favour of treatment A; thereby, rejecting the null hypothesis (105). In rheumatology research, superiority RCTs are often used to evaluate efficacy e.g. comparing a new biological drug to methotrexate (MTX) or even placebo among patients with IA. However, one could argue that the comparison is not optimal as patients with IA who qualify for biological therapy not are expected to be sufficiently treated with MTX and even less with placebo. A more ideal trial design would be a head-to-head comparison of the new biological drug to an established biological drug with the aim not to demonstrate superiority but equivalence or non-inferiority. Figure 1.1 provides an overview of the different types of RCTs.

Figure 1.1. Schematic presentation of the different types of randomised controlled trials.
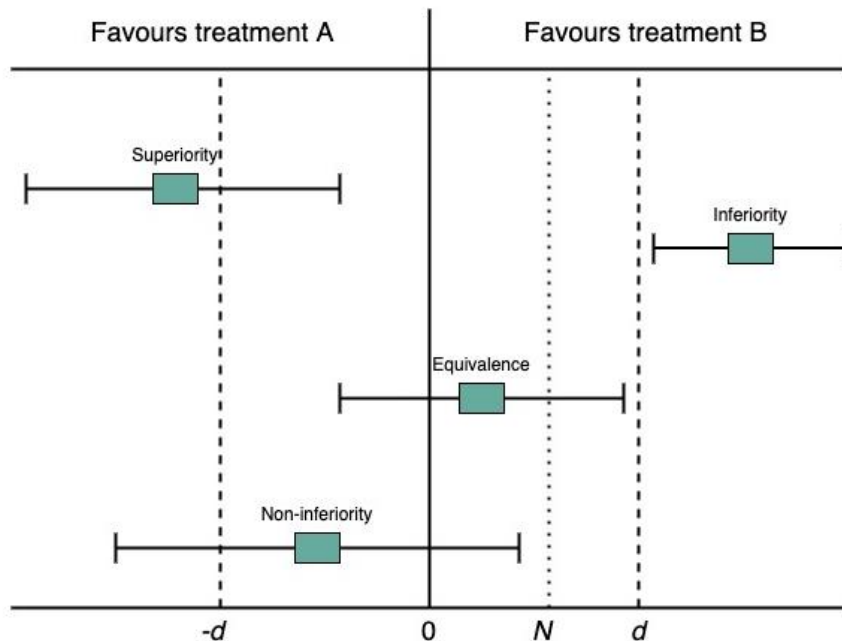
Green boxes represent the estimated difference between treatment A and B, error bars indicate the 2-sided 95% confidence interval, the interval -d to d is the equivalence range, and N is the non-inferiority margin.

Equivalence RCTs aim to establish if treatment A has a similar enough effect compared to treatment B and is relevant when treatment A e.g. is less expensive, has fewer side effects or is easier to administer (105,106). Before initiation of the study, an interval of equivalence (based on the available evidence and clinical judgement) must be defined. Acceptable similarity can be claimed if the 95% confidence interval (95% CI) for the difference in treatment effect lies within the pre-specified equivalence margins.

Non-inferiority RCTs evaluate if treatment A not is unacceptably worse than treatment B; thus, the non-inferiority trial is by definition one-sided (105,106). A non-inferiority margin must be defined (based on the available evidence and clinical judgement) before the study is initiated. Non-inferiority is proven if the lower bound of the 95% CI for the difference in treatment effect does not cross the non-inferiority margin. Moreover, if non-inferiority is proven, a superiority test can be performed to

evaluate if treatment A in fact is better than treatment B (which cannot be done in an equivalence trial) (105).

When choosing between conducting an equivalence or a non-inferiority study, the important question is if both ends of the 95% CI of the difference in treatment effect is of interest. Thus, is it essential to evaluate if treatment A not is better and not is worse than treatment B (equivalence) or is it sufficient to assess if treatment A not is worse than treatment B (non-inferiority). Furthermore, as the non-inferiority trial is one-sided, a smaller sample size is required compared to an equivalence trial which would result in fewer resources and costs needed to conduct the study.

1.7.2. DESIGNS OF DOSE REDUCTION TRIALS

RCTs evaluating dose reduction of biologics are aiming to assess if disease activity at the end of the study is comparable between the tapering group/withdrawal group (despite biologics dose reduction/interval prolongation/discontinuation) and the continuation group. As the study population consist of patients in sustained remission or LDA, a higher proportion of arthritis flare is expected in the intervention group as a consequence of reducing the biologic dose/prolonging the biologic dosing interval/complete biologic withdrawal. Thus, a superiority RCT design is not the optimal choice for a dose reduction trial as tapering/withdrawal due to the increased risk of arthritis flare not is likely to be superior to continuation of biologic standard dose when evaluating disease activity. A recent Cochrane review on TNFi dose reduction in RA support this rationale and recommended to limit superiority analyses for domains where superiority can be expected e.g. infection rates and costs (103).

A more optimal study design would be an equivalence study aiming to assess if biologic dose reduction not is any better and any worse than continuation of biologic standard dose. However, as an equivalence study require a large sample size, a non-inferiority study evaluating if biologic dose reduction not is any worse than continuation of biologic standard dose is often sufficient. Thus, Cochrane recommend the non-inferiority approach over the superiority design as dose reduction trials aim to maintain (not improve) disease activity while minimising the use of biologics (103).

CHAPTER 2. HYPOTHESES AND AIMS

2.1. HYPOTHESIS

The overall hypothesis of this dissertation is that patients with IA treated with biological therapies and in sustained remission or LDA can reduce dose of their biological treatment and maintain stable disease activity.

2.2. AIMS

This dissertation aims to evaluate the hypothesis by:

- Estimate the risk of flare in a systematic literature review (SLR) and meta-analysis based on randomised, controlled trials evaluating tapering or withdrawal of b-/tsDMARDs in patients with IA in sustained remission or LDA compared to continuation of standard dose (**Study I**)
- Investigating in a randomised trial if a disease activity-guided tapering algorithm for biologics compared to biologic continuation in patients with IA in sustained LDA will enable a significant proportion to reach ≥50% biologic dose reduction while equivalent disease activity remains (**Study II**)
- Identify potential baseline predictive factors for successful biologic tapering based on data from Study II (**Study III**)

CHAPTER 3. PRESENTATION OF STUDIES

3.1. STUDY I (PAPER I)

3.1.1. STUDY OBJECTIVES

The objective of study I was to estimate the risk of arthritis flare among patients with IA in sustained remission or LDA who taper or withdraw b- or tsDMARDs compared to continuation of the treatments.

3.1.2. STUDY DESIGN, POPULATION AND METHODS

Study I was a SLR, registered at PROSPERO (CRD42019136905), and carried out in accordance with recommendations from the Cochrane Collaboration (107) and the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) (108). A systematic search was conducted in four databases (Cochrane Library, PubMed, EMBASE and Web of Science); moreover, recent EULAR and ACR congress abstracts were assessed for eligibility. RTCs evaluating tapering or withdrawal of b- or tsDMARDs with continuation of standard dose among patients with IA were eligible if follow-up was ≥ 24 weeks.

A restricted maximum likelihood (REML) mixed-effects model was applied for the meta-analyses to take between study variance into consideration. Risk ratio (RR) with 95% CI was applied for the primary outcome flare (109); whereas, Peto's Odds Ratio (POR) with 95% CI was used for the secondary outcomes due to sparse events (110). To evaluate tapering versus withdrawal, a network meta-analysis was performed which takes both direct comparison and indirect comparisons across RTCs based on a common comparator (continuation of biologics) into consideration (111). A more detailed description of the study is provided in Appendix A (Paper I).

3.1.3. RESULTS

Twenty-two studies were included in the meta-analyses; study selection is illustrated in Appendix A (Paper I, Figure 1). The study population contained data on 4,082 patients with RA and 831 patients with axSpA; thus, no studies in patients with PsA were identified. Important study characteristics, risk of bias assessment and certainty of the evidence are described in Appendix A (Paper I, Table 1 and Table 2).

Tapering versus Continuation

Fifteen trials had available data on flare: eleven trials on TNFi (76–79,112–118), one trial on interleukin-6 inhibitor (IL6i) (119), one trial on B-cell depletion (120), one trial on co-stimulation blocker (121), and one trial on JAKi (122). An increased flare risk was observed: RR = 1.45 (95% CI: 1.19 to 1.77).

Persistent flare was pre-defined as flares with no improvement despite b-/tsDMARDs dose escalation or glucocorticoid treatment. Eight trials had available data: six trials on TNFi (76,79,112,116–118), one trial on B-cell depletion (120), and one trial on JAKi (122). The odds for persistent flare was only potentially increased: POR = 1.56 (95% CI: 0.97 to 2.52).

Withdrawal versus Continuation

Eleven studies had available data on flare: however, the only mode-of-action was TNFi (112,116–118,123–129). The risk of flare was significantly increased: RR = 2.28 (95% CI: 1.78 to 2.93).

Seven trials with TNFi as mode-of-action had available data on persistent flare: (112,116–118,124,126–128). The odds for persistent flare were highly increased: POR = 3.41 (95% CI: 1.91 to 6.09).

Network meta-analysis

Figure 3.1 provide an overview of studies included in the network meta-analyses. When comparing withdrawal to tapering, a highly increased odds for flare, odds ratio (OR) = 5.62 (95% CI: 3.44 to 9.17), as well as persistent flare, OR = 3.16 (95% CI: 1.49 to 6.67), was demonstrated.

Safety measures

No significant difference in safety measures was demonstrated, Appendix A (Paper I, Table 2).

Figure 3.1. Network diagrams for the outcomes: A) Flare and B) Persistent flare.
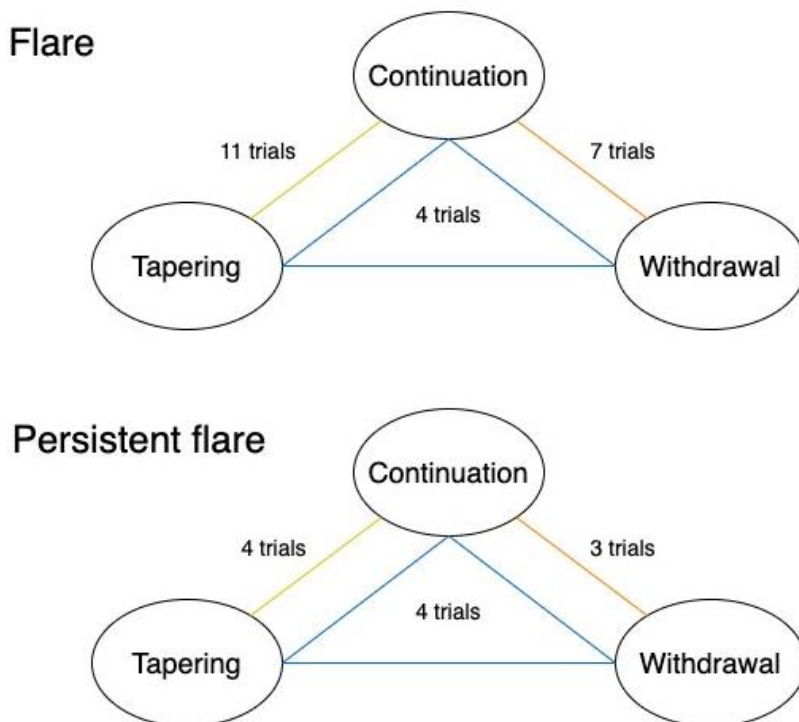
Green line: two-arm studies comparing tapering to continuation, orange line: two-arm studies comparing withdrawal to continuation, and blue triangle: three-arm studies comparing tapering, withdrawal and continuation.

3.1.4. METHODOLOGICAL CONSIDERATIONS

Study I is the first SLR and meta-analysis to evaluate flare after b-/tsDMARDs tapering or withdrawal of among patients with IA. The main strengths are the high level of evidence in the study design i.e. SLR and meta-analysis based on RCTs which is more likely to give an unbiased estimate of the intervention effect. One could argue that inclusion of observational studies, representing a 'real world setting', would provide additional valuable information. However, a Cochrane review did not find significant differences in the effect estimate between RCTs and observational studies (130). Thus, the Cochrane Collaboration generally recommend only to include observational studies in SLR when no RCTs are available as potential bias are likely to be greater in observational studies (107). Only RCTs were included in this SLR to minimise the risk of potential bias; however, as no RCTs

were identified in patients with PsA, inclusion of observational studies could provide valuable information on the intervention effect in this population.

Another strength of this work is that a network meta-analysis was applied to evaluate tapering versus withdrawal; thereby, providing an indirect estimate of the risk for flare and persistent flare among patients with IA. As a network meta-analysis exploit all available evidence, the method usually provides a more precise estimate of the intervention effect than a single direct or indirect estimate (107).

However, there are limitations to discuss as no studies with data on PsA were identified; thus, the findings of this SLR only comply to patients with RA and axSpA. Moreover, the number of studies in RA was much larger than axSpA (17 versus 5 studies) but sub-group meta-analysis did not reveal any significant difference in flare risk between the two diagnosis, Appendix A (Paper I).

The majority of the included studies only had data on TNFi (18 out of 22 studies); thus, limited data were available on other modes of action. Potential differences in flare risk among the different b-/tsDMARDs were evaluated in sub-group meta-analyses (Appendix A [Paper I]); however, as data were sparse for all other modes-of-action than TNFi no define conclusion can be drawn.

Another limitation to discuss is the heterogenous flare criteria in the included trials as validated flare criteria first was published after several trials were initiated (published in 2013 for RA (70) and in 2018 for axSpA (71)). However, the flare criteria in the individual studies were assessed to be adequate and reasonable for measuring flare by the independent assessors (Appendix A [Paper I]); thereby, allowing assessment of the intervention effect across trials.

Lastly, different tapering strategies were used in the included trials; therefore, potential differences in the flare risk were explored in a sub-group meta-analysis. The flare risk appeared to be highest in trials with the more aggressive disease-activity guided tapering strategy than in trials with a fixed dose reduction strategy. Additional methodological considerations are described in detail in Appendix A (Paper I).

3.1.5. CONCLUSION

Withdrawal of TNFi among patients with RA or axSpA in sustained remission/LDA results in a highly increased risk of flare and persistent flare compared to continuation of standard dose. Therefore, tapering seems to be a more favourable approach as a significantly increased risk only was observed for flare and not for persistent flare when b-/tsDMARDs was tapered versus continued.

3.2. STUDY II (PAPER II & PAPER III)

3.2.1. STUDY OBJECTIVES

The objective of study II was to assess if a disease activity-guided tapering algorithm for biologics compared to biologic continuation allowed a significant proportion to reach ≥50% biologic dose reduction at 18 months while equivalent disease activity was maintained.

3.2.2. STUDY DESIGN, POPULATION AND METHODS

Study II was designed as an 18-month long pragmatic, multicenter, randomised controlled, open-label, equivalence trial (EudraCT: 2017-001970-41). As previously reported (Appendix B [Paper II]), the trial was approved by the Danish Medicine Agency (2017091722), the ethics committee of The North Denmark Region (N-20170073), and the Danish Data Protection Agency (2017-194). Furthermore, the study was monitored by Good Clinical Practice (GCP) inspectors.

Eligible patients were ≥18 years old and diagnosed with RA based on the ARA 1987 criteria (2) or the ACR/EULAR 2010 criteria (3), PsA according to the Moll and Wright 1973 criteria (4) or the 2006 CASPAR criteria (5), or axSpA based on the ASAS 2009 classification criteria (6) or the Modified New York AS 1984 criteria (7). Furthermore, patients had to be in LDA and on stable dose abatacept, TNFi, or tocilizumab during ≥12 months. Treatment with oral, parenteral, or intra-articular corticosteroids within the last 12 months was not allowed. After written, informed consent was obtained, participants were randomised in ratio 2:1 to either the tapering group or the continuation group.

Participants in the tapering group prolonged the dosing interval of their biological therapy after a disease activity-guided tapering algorithm until flare or complete withdrawal. The tapering algorithm is described in detail in Appendix B (Paper II). Participants in the continuation group was kept on their baseline biological dose; however, as usual practice in Denmark a small increase in the dosing interval was allowed if requested by the patient.

Patients were monitored at 4, 8, 12 and 18 months from baseline and at additional visits if symptoms of flare occurred. As described in Appendix B (Paper II) and Appendix C (Paper III), flare was defined by:

- RA and PsA: ΔDAS28-CRP >1.2 or ΔDAS28-CRP >0.6 AND a current DAS28 ≥3.2 (70).
- AxSpA: ΔASDAS ≥0.9 (71), inflammatory back pain and/or ≥1 swollen joint.

The primary objective was met if a significant difference in patients on ≥50% reduced biologic dose at 18 months was demonstrated between the trial groups while an equivalent disease activity state was maintained.

Appendix B (Paper II) provide a more detailed description of the study methods and statistical analyses.

3.2.3. RESULTS

One-hundred-and-forty-two patients were enrolled between May 2018 and March 2020; thus, the target population of 180 included patients was not reached. The recruitment period was closed in April 2020 due to the national implications of the coronavirus 19 pandemic. A flow-diagram of participant recruitment with reason for exclusion is presented in Appendix C (Paper III). The tapering group comprised of 95 patients and the continuation group of 47 patients.

At 18 months, a significant difference in dose reduction was observed as 35 patients (37%) in the tapering group had reduced their biologics by ≥50% compared to one patient (2%) in the continuation group, absolute risk difference (RD) 35% (95% CI: 24% to 45%). Disease activity at 18 months was equivalent between the two groups as the 95% CI for the mean difference (95% CI: -0.12 to 0.29) was within the limits of the pre-specified equivalence margin of ±0.5 disease activity points. Thus, the primary objective was proven.

Biologic dose reduction by interval prolongation was possible in a total of 70 patients (74%) in the tapering group of which 14 patients (15%) managed to completely withdraw their biological therapy. Only 8 patients (17%) in the continuation group had optimised their biological treatment at 18 months follow-up.

Flare in accordance with the pre-specified flare criteria was more frequent in the tapering group (39 [41%]) compared to the continuation group (10 [21%]), the risk difference was significant: 20% (95% CI: 4% to 35%). Similarly, significantly more patients in the tapering group experienced symptoms of flare but did not fulfil the flare criteria (38 [40%] vs 6 [13%], respectively), RD: 27% (95% CI: 14% to 41%). However, flares were managed with rescue therapy, such as biologic dose escalation or glucocorticoids, as non-reversable (persistent) flare only occurred in one patient (1%) in the tapering group and three patients (6%) in the continuation group. These patients were switched to another biological drug.

The frequency of adverse events and serious adverse events was comparable between the tapering group and the continuation group.

3.2.4. METHODOLOGICAL CONSIDERATIONS

Study II is first to evaluate disease activity-guided tapering of biologics in a RCT with a study population of IA. The main strength is the randomised design with a co-primary endpoint aiming to demonstrate first superiority in the proportion of patients achieving ≥50% biologic reduction in favor of the tapering group; thereafter, equivalent disease activity at 18 months. Thus, as discussed in the introduction of this thesis, study II complies with the recommendation by the Cochrane Collaboration as a superiority approach not was used to evaluate disease activity but limited to domains where superiority could be expected (103).

Other important strengths are the investigator-initiated aspect (i.e., no pharmaceutical industry involvement), the pragmatic tapering algorithm which is easy to implement in clinical practise, and similar assessments of the trial groups throughout the study period. Furthermore, the study population represented real-life patients from routine care as less strict in- and exclusion criteria were applied, the study drug included biologics with different modes-of-action, and treatment with various concomitant medications as well as previous biologic failure history was allowed. Thus, the generalisability of study II is judged to be high.

Another strength is that study II complies with the 'Consolidated Standards of Reporting Trials' (CONSORT) statements (104,106); thereby, ensuring transparency. As recommended by CONSORT, the primary and secondary outcomes were analysed both as intention-to-treat (ITT) and as per protocol. Results were similar between the two methods as the number of patients lost to follow-up or not adhering to the protocol were kept to a minimum.

An important limitation to discuss is that study II was slightly underpowered as the inclusion period was closed before the target population was reached due to the national implications of the coronavirus 19 pandemic. In an attempt to reach the target sample size, the eligibility criteria was altered during the study period to allow enrolment of patients in baseline LDA as well as baseline remission. The alteration was based on findings by Tweehuysen et al. as baseline disease activity not was identified as an important predictor for successful biologic tapering in patients with RA (102). As presented in Appendix A (Paper I) and in Table 1.7 to 2.0, baseline LDA was also used as an inclusion criteria in some previous dose reduction studies in patients with IA. A possible advantage to the alteration is that baseline LDA in stead of baseline remission will allow for a study population who resemble the real-world outpation population better; thereby, increasing the trial generaibility.

The co-primary endpoint 'disease activity' was evaluated with an equivalence approach to assess if disease activity in the tapering group at 18 months was no worse and no better than disease activity in the continuation group. The equivalence approach was choosen over non-inferiority as increased patient satisfaction and

health-related quality of life previously have been reported when fewer drug doses are required to manage a disease (131). Thus, disease activity could potentially improve in the tapering group due to lower PROM scores (e.g. Patient Global Health Visual Analogue Scale [VAS]). But as described above, the target sample size was not reached and therefore the trial is underpowered. Similarly, the STARSS trial neither reached the target sample size due to enrolment difficulties (79). Thus, a non-inferiority approach which requires a smaller sample size would have been more preferable; an important consideration to keep in mind when future tapering studies are planned.

The internationally accepted and validated flare criteria for RA and axSpA were used in BIODOPT i.e., the DAS28-based criteria (70), and the ASDAS-based criteria (71), respectively. However, '≥1 swollen joint' was added to the ASDAS-based flare criteria to capture peripheral arthritis flare and 'inflammatory back pain' was added in an attempt to qualify that an ASDAS worsening indeed was due to arthritis flare. As described in the introduction of this thesis, no flare criteria is yet defined for PsA; therefore, a pragmatic approach was applied where patients with predominant peripheral PsA were evaluated after the DAS28-based flare criteria and patients with predominant axial PsA were assessed using the ASDAS-based flare criteria (Appendix B [Paper II] & Appendix C [Paper III]). Although not optimal, this approach was judged by expert opinion to be the best alternative as no consistent PsA flare criteria have been used in the literature as presented in Table 1.7 and 2.0.

Lastly, another potential limitation to discuss is that patients not were monitored with x-ray or magnetic resonance imaging (MRI) during the study. However, the ADOPT trial and the DOBIS trial recently demonstrated that clinical flare criteria identified 102 out of 104 flaring RA patients and 106 out of 107 flaring axSpA patients during disease activity-guided tapering of biologics (132,133). In both studies, one patient only had flare on MRI whereas one patient only progressed on radiographs in the ADOPT study (133). The DOBIS trial and a recent SLR did not report considerable radiographic progression for TNFi tapering in patients with axSpA (132,134); thus, the added value of radiographs in study II for patients with axSpA would probably be minimal. However, a recent Cochrane SLR found disease activity-guided TNFi tapering in patients with RA to potentially increase the risk of minimal radiographic progression, RR: 1.45 (95% CI: 0.77 to 2.73, low-quality evidence) (103). Therefore, radiographs in patients with peripheral disease could contribute with valuable information on possible radiographic progression during biologic tapering. Additional methodological considerations are described in detail in Appendix B (Paper II) & Appendix C (Paper III).

3.2.5. CONCLUSION

Disease activity-guided tapering of biologics compared to biologic continuation in patients with IA allowed significantly more patients to reach ≥50% biologic dose reduction (by interval prolongation) at 18 months while an equivalent disease activity state was maintained. Even though flares were more frequent in the tapering group, flares were managed with rescue therapy as no significant risk of persistent flare (i.e. loss of therapeutic response) was observed.

3.3. STUDY III (PAPER IV)

3.3.1. STUDY OBJECTIVES

The objective of study III was to identify potential predictive factors for successful biologic tapering from baseline characteristics based on data from Study II.

3.3.2. STUDY DESIGN, POPULATION AND METHODS

These secondary analyses were based on data from Study II. The study design, patient population and intervention has been described in detail in the methods section of Study II as well as in Appendix B (Paper II) and Appendix C (Paper III).

The study population comprised of the ITT population. As described in Appendix D (Paper IV), successful tapering was pre-defined as: patients without protocol deviations, on ≥50% reduced biologic dose, and in LDA (DAS28-CRP ≤3.2 for RA and PsA and ASDAS <2.1 for axSpA) at 18 months. A conservative approach assuming trial failure was applied for missing data on the dependent variable (successful tapering).

Modified Poisson regression with robust variance estimator was applied for the regression analyses. The clinical-driven multivariable model included variables judged to be of significantly importance by expert opinion: tapering group, female sex, age, repeated biologic failure (on biologic number ≥3), and baseline remission. The data-driven multivariable model included variables with a univariate p-value <0.10. Model validity was assessed by the cross-validated area under the receiving operator characteristic curve (AUC).

3.3.3. RESULTS

One-hundred-and-forty-two patients were randomised to the tapering group (n=95) or the continuation group (n=47) of which 32% (30/95) and 2% (1/47) achieved successful biologic tapering with a dose reduction ≥ 50% while maintaining LDA at 18 months. Moreover, an additional 32% (30/95) of patients in the tapering group and 13% (6/47) of patients in the continuation group tapered their biologic dose <50% and maintained LDA.

Tapering group, Health Assessment Questionnaire Disability Index (HAQ-DI), pain VAS, fatigue VAS, patient global health VAS, Short Form Health Survey 36 (SF-36) Physical Component Summary (PCS), SF-36 Mental Component Summary

(MCS) demonstrated significant univariate association with achieving successful tapering at 18 months as presented in Appendix D (Paper IV). The data-driven multivariable regression analysis only identified tapering group, RR: 14.0 (95% CI: 1.9 to 101.3, p=0.009) as predictive for successful tapering; nonetheless, higher SF-36 MCS was considered to be an important nonsignificant predictor, RR: 1.06 (95% CI: 0.99 to 1.13, p=0.097). The cross-validated AUC of 0.72 (95% CI: 0.63 to 0.82) for the data-driven model corresponds to reasonable prediction. In the clinically-driven regression model, tapering group was the only independent predictor, RR: 14.9 (95% CI: 2.1 to 107.1, p=0.007) and the model demonstrated poor prediction with an AUC of 0.47 (95% CI: 0.38 to 0.57).

3.3.4. METHODOLOGICAL CONSIDERATIONS

Study III is the first to explore data from a RCT study in the attempt to identify potential predictors for successful tapering of biologics in patients with IA. Strengths and limitations to the BIODOPT trial have been discussed in the previous section and in Appendix B (Paper II) and Appendix C (Paper III).

The main strengths of this secondary analysis are that data was analysed and reported in accordance with the 'Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis' (TRIPOD) recommendation (101,135). Thus, continuous variables were kept continuous as categorisation leads to information loss, particularly if the continuous variable is dichotomised. Moreover, as recommended by TRIPOD continuous variables were evaluated for a linear functional relationship with the outcome (i.e. successful tapering) as non-linearity would lead to an incorrect model if not handled (101,135). In this study, non-linearity was observed for the variable tender joint count; therefore, the variable was categorised.

Another significant strength to this study is that variables included in the multivariable regression models were assessed for correlation as highly correlated variables may lead to a decreased signal. Pain VAS, Fatigue VAS, and Patient Global Health VAS were highly correlated and therefore handled by treelet transformation in the sensitivity analysis for the data-driven regression model.

As recommended in the TRIPOD statement (101,135), internal validation was evaluated by cross-validation for the multivariable regression models. Assessment of internal validation is important as prediction models tend to be overfitted which leads to an optimistic performance (135). In this study, the data-driven model demonstrated acceptable prediction whereas the clinical-driven model yielded poor prediction.

An important limitation to discuss is the reduced statistical power which was a consequence of not reaching the target population due to the national implications of the coronavirus-19 pandemic. This increases the risk of type II errors i.e. failure to identify other relevant predictors for successful tapering. Thus, caution must be applied when evaluation the trial results.

Another possible limitation to consider is the method used for predictor selection i.e. univariate p<0.10 in the data-driven model and pre-selected variables considered to be of particular importance in the clinical-driven model. These methods are both commonly used for multivariable regression models but comes with the risk of rejecting potentially important predictors (i.e. type II error) due to a nonsignificant univariate association or variables not pre-specified as particular important. However, the methods used for predictor selection in this study were judged by statistical experts, who participated in analyses of the trial data, to be reasonable when considering the size of the data set and the frequency of the outcome i.e. patients achieving successful tapering. In a larger data set backwards elimination would probably be a more optimal method for predictor selection.

It could also be considered a limitation that disease specific baseline variables not were included in this study e.g. rheumatoid factor and DAS28-CRP for patients diagnosed with RA. However, this was a consequence of the reduced statistical power due to the sample size which would result in a significant lack of power if disease specific variables were to be assessed.

3.3.5. CONCLUSION

Disease activity-guided tapering can reduce the biologic dose markedly ($\geq 50\%$ compared to baseline) without deterring disease activity in approximately one third of patients tapering biologics. Moreover, an additional one third of patients in the tapering group had reduced their biologic dose <50% and maintained LDA at 18 months. Thus, disease activity-guided tapering is judged to be a feasible tool for tapering biological therapies in patients with IA. Tapering group was the only independent predictor for successful tapering but better baseline mental health (higher SF-36 MCS) was considered to be an important nonsignificant predictor in the data-driven model. Caution must be applied when evaluating the results as future research is needed to provide additional insight into predictors across IA diagnoses. However, assessment of metal health by the SF-36 survey could provide additional insight to the physician and the patient when tapering is considered.

CHAPTER 4. DISCUSSION

4.1. THE OVERALL FINDINGS

The overall aim of this dissertation was to evaluate dose reduction of biological therapies compared to continuation of biologics among patients with IA in sustained remission or LDA. The three presented studies attempts to answer this research question. The overall findings of this dissertation are:

- Based on data from RCTs with a study population of RA and axSpA, biologic withdrawal compared to biologic continuation had a highly increased risk for flare and persistent flare whereas biologic tapering only had a significantly increased risk for flare and not for persistent flare.
- In a RCT, disease activity-guided tapering of biologics was found to be effective and safe to achieve a considerable dose reduction while maintaining equivalent disease activity.
- Better baseline mental health status was identified as a potentially important nonsignificant predictor for achieving successful biologic tapering.

4.2. DOSE REDUCTION OF BIOLOGICS

When evaluating the evidence of biologic dose reduction, the majority of studies evaluate fixed dose reduction as only few studies on disease activity-guided tapering have been conducted as presented in Appendix A (Paper I) and in this thesis. Moreover, the available studies predominantly have a RA population and evaluate a limited number of biologics, most often only TNFis. These characteristics were also seen in Study I as only two out of 23 trials evaluated disease activity-guided tapering, 17 trials had a RA population, five trials an axSpA population, and only four out of 23 trials assessed tapering of a non-TNFi. Study I found TNFi withdrawal to have a highly increased risk for flare and persistent flare when compared to TNFi continuation. Interestingly, b-/tsDMARDs tapering only demonstrated a significantly increased risk for flare and not for persistent flare when compared to b-/tsDMARDs continuation; therefore, the strategy was judged to be more favourable than withdrawal. The findings in study I is comparable to recent reports in SLRs based on RCTs and/or observational studies with a RA population as biologic withdrawal leads to an increased risk of loss of remission or LDA compared to biologic continuation and therefore seem to be an inferior strategy whereas biologic tapering seem to be comparable to biologic continuation (103,136–139). In axSpA, Study I and another SLR (which included RCTs and observational studies) have reported a high risk for flare when TNFis were withdrawn whereas

TNFi tapering seemed to be comparable to TNFi continuation as no increased risk of persistent flare were observed and stable disease activity was maintain in the majority of patients (140). However, the evidence in axSpA is a bit conflicting as a recent SLR by Lawson et al. beside an increased risk for flare also reported an increased risk of BASDAI worsening, of not reaching ASAS 40% improvement, and of not achieving ASAS partial remission (141). A possible explanation for the observed difference could be that different dose reduction strategies were pooled in the study by Lawson et al. as one large study evaluated withdrawal, another large study assessed on demand treatment, and four small to midsize studies evaluated fixed-dose reduction. Off note, the mean difference in BASDAI of 0.35 (95% CI: 0.10 to 0.60) between dose reduction and continuation observed in the study by Lawson et al. was statistically significant but within the minimal clinical important difference of ±1.0 (142). The evidence for biologic dose reduction in patients with PsA is limited as fewer studies have been conducted as previously described. A SLR by Ye et al. based on smaller observational studies found biologic withdrawal in patients with PsA to have a substantial risk of loss of disease control (143). Biologic tapering was judged to potentially be feasible and safe as stable disease control seemed to be maintained for a prolonged period of time.

Very recent, a RCT evaluating fixed dose tapering of etanercept in patients with RA, PsA or axSpA with sustained minimal disease activity (MDA) have been published (144). The tapering group doubled the dosing interval whereas the continuation group maintained etanercept standard dose. At 6 months, 77% (62/81) of patients in the tapering group had maintained the 50% interval prolongation whereas the remaining had stepped back to standard dose. No significant difference in MDA frequency was observed between the tapering group (63%, [47/75]) and the continuation group (74%, [56/76]) nor between the different IA diagnoses. Patients in MDA at month 6 either withdrew etanercept (tapering group) or doubled the etanercept dosing interval (control group). Thus, at 12 months follow-up 40% (20/50) of patients in the tapering group maintained MDA despite etanercept withdrawal whereas 53% (33/58) of patients in the continuation group maintained MDA despite doubling the etanercept dosing interval. Thus, the trial confirms previous findings as presented above i.e., fixed dose tapering of biologics is possible for a substantial proportion of patients across different IA diagnoses while an acceptable disease activity state is maintained. For a considerable proportion of the patients, total etanercept withdrawal was possible. Moreover, patients who had flared during the study reached an acceptable disease activity state after reinstatement of etanercept standard dose; thus, comparable to previous findings as presented in the Appendix A (Paper I), and in this thesis. Reassuringly, only one patient (with PsA) from the tapering group had persistent flare and was switched to another biological therapy (144).

Recent congress abstracts from the ARCTIC REWIND TNFi trial evaluated TNFi continuation vs fixed dose tapering to half-dose TNFi for 4 months followed by

TNFi withdrawal in patients with RA in sustained remission (145,146). At 12 months follow-up, similar disease activity was observed between the trial groups despite the difference in TNFi dose; thus, as previously discussed comparable findings to other studies. However, the abstracts lack information on the rates of patients in the tapering group who were able to withdraw or taper their TNFi and patients who received re-treatment with TNFi standard dose due to flare. Thus, the results must be interpreted with caution until greater details have been reported in the final paper.

The recent PREDICTA trial had a study population of RA in sustained remission on adalimumab who were randomised to adalimumab tapering by a 25% interval increase or to adalimumab withdrawal (147). At 36 weeks follow-up, 64% (65/102) of patients in the tapering group and 55% (11/20) of patients in the withdrawal group had not experienced a flare. Time-to-flare was longer in the tapering group compared to the withdrawal group as the first quartile, corresponding to the timepoint where 25% had experienced a flare, was 18.0 weeks compared to 13.3 weeks, respectively. A similar time-to-flare pattern have been reported previously in other RCTs (116,118,122,124,127). In PREDICTA, remission was regained after adalimumab rescue therapy in 38% (11/29) of patients in the tapering group and 50% (4/8) of patients in the withdrawal group at 36 weeks follow-up; thus, lower than reported in most RCTs: withdrawal group ~70% regained remission (follow-up: 26 or 48 weeks) (124,127), tapering group 41-75% regained remission (follow-up: 12 or 18 months) (79,121). A possible explanation for the observed difference in remission rate in the tapering group after rescue therapy could be the longer time-to-flare combined with the short follow-up period in PREDICTA. Furthermore, the low number of patients receiving rescue therapy contributes with some uncertainty to the estimates. An important aspect to keep in mind is that most patients in previous RCTs regain LDA after rescue therapy: withdrawal group 85-96% (follow-up: 26 or 48 weeks) (124,127), tapering group 73-80% (follow-up: 48 weeks to 18 months) (79,122).

The recently published COAST-Y trial evaluated ixekizumab continuation vs ixekizumab withdrawal in patients with axSpA in remission (148) and reported results similar to previous studies as presented in Appendix A (Paper I) and in this thesis. Thus, at 40 weeks follow-up 83% (85/102) of patients in the continuation group and 55% (29/53) of patients in the withdrawal group had not experienced a flare. In patients who flared and received rescue therapy, 44% recaptured remission and 93% recaptured LDA in the withdrawal group compared to 30% and 50% in the continuation group, respectively. Thus, acceptable disease activity was captured after ixekizumab re-treatment consistent to findings from previous studies. The lower rate of recaptured remission and LDA in the continuation group is most likely due to loss of treatment effect.

As previously discussed, important differences exists among the different trials evaluating dose reduction of biological therapies. In study I, the included studies was observed to have differences in disease duration, criteria for and duration of remission or LDA before initiating dose reduction, tapering strategy, duration of the study period, pharmaceutical industry funding, and overall risk of bias. The effect of these differences was explored in sub-group meta-analyses (Appendix A [Paper I]) which only revealed a significantly increased flare risk for studies with >28 weeks follow-up, and a significantly increased risk for flare and persistent flare in studies with a higher overall risk of bias when TNFi withdrawal was compared to TNFi continuation. Furthermore, the evaluated b-/tsDMARDs were observed to have flare risk differences but as data per drug were sparse, no define conclusion can be drawn. Differences in flare criteria between trials were also observed in Study I as validated flare criteria for RA and axSpA only recently have been published, 2013 (70) and 2018 (71) respectively. However, as described in Appendix A (Paper I) the independent assessors found the flare criteria similar enough to allow comparison across trials. Thus, the potential effect of the between study heterogeneity was taken into consideration in study I when the evidence for dose reduction across trials and across different IA diagnoses was compared.

Based on the current evidence from RCTs and observational studies across IA diagnoses, dose reduction of biologics is feasible across different IA diagnoses with the strongest evidence in RA. Based on evidence from meta-analyses, tapering seem to be a more favourable dose reduction strategy than biologic withdrawal.

4.3. DISEASE ACTIVITY-GUIDED TAPERING OF BIOLOGICS

Different strategies for biologic tapering exist as described in the introduction of this thesis. Disease activity-guided tapering is generally acknowledged as the more aggressive tapering strategy as dose reduction is continued in accordance with the algorithm until flare or complete withdrawal. The evidence for disease activity-guided tapering of biologics are currently limited to a few RCTs (76,79,149) and a handful of observational studies (97,132,133,150,151). Study II is the first RCT to evaluate disease activity-guided tapering of biologics across IA diagnoses and found that 74% (79/95) of patients in the tapering group were able to space the biologic dosing interval. Similarly, biologic interval prolongation was possible for 75% (48/64) and for 63% (76/121) of patients with RA tapering adalimumab or etanercept in the STRASS (79) and the DRESS trial (76), respectively, for 62% (87/141) of patients with RA tapering biologics in the ADOPT trial (133), for 52% (55/106) of patients with axSpA tapering TNFi in the DOBIS trial (132), and for 53% (31/58) of patients with AS tapering adalimumab, etanercept or infliximab in a study by Arends et al. (97). In study II, equivalent disease activity was demonstrated between the tapering group and the continuation group despite the difference in

biologic dose. This finding is in line with previous studies who reported disease activity to remain low despite disease activity-guided tapering (76,97,132,133,150,151). However, disease activity between groups was observed to be significantly different in the STRASS trial and therefore equivalence could not be proven (79).

In study II, 15% (14/95) of patients in the tapering group managed to discontinue their biological therapy; per diagnosis this corresponded to 17% (7/41) of patients with RA, 17% of patients with PsA (3/18), and 11% (4/36) of patients with axSpA. Thus, the rate of patients with RA able to withdraw their biologics were comparable to previous findings in the DRESS trial (20% [24/121]) (76) and the ADOPT trial (16% [22/141]) (133) but significantly lower than in the STRASS trial (39% [25/64], Fisher's exact test: p=0.018) (79). For patients with axSpA, significantly more patients in the BIODOPT tapering group could withdraw their biological therapy compared to the DOBIS trial (1% [1/106], Fisher's exact test: p=0.015) (132) and the study by Arends et al. (0% [0/58], Fisher's exact test: p=0.019) (97).

As previously described, flare criteria varies between studies as validated criteria for RA and axSpA only recently have been published, 2013 (70) and 2018 (71) respectively, and no flare criteria exists for PsA. In study II, statistically significant more patients in the tapering group (41% [39/95]) compared to the continuation group (21% [10/47]) had a flare in accordance with the pre-specified flare criteria, RD: 20% (95%CI: 4% to 35%). Moreover, considerably more patients experienced symptoms of flare but did not fulfil the flare criteria: tapering group 40% (38/95) and continuation group 13% (6/47), RD: 27% (95%CI: 14% to 41%). Similarly, the DRESS trial and STRASS trial reported statistically significant higher flare rates in the tapering group compared to the continuation group, DRESS: 73% (88/121) vs 27% (16/59) (76), STRASS: 77% (49/64) vs 47% (34/73) (79). High flare rates were also observed in the ADOPT trial (87% [122/141]) (133) and in the DOBIS trial (98% [107/109]) (132). In the study by Arends et al., 43% (25/58) returned to TNFi standard dose due to recurrence of disease activity judged by the patient and/or physician (no flare criteria was defined). Recently, Zhang et al. evaluated disease activity-guided tapering of an etanercept biosimilar in patients with AS in remission or LDA for 12 weeks (149). Flare rates were non-significantly higher for patients in initial LDA compared to initial remission (17% [12/72] vs 9% [8/89], Fisher's exact test: p=0.157) but considerably lower than observed in other disease activity-guided tapering trials. A possible explanation for the low flare rates in the study by Zhang et al. could be the relative short study period of 36 weeks with only 12 weeks of follow-up after the last dose reduction. Similar to the study by Zhang et al., study II and study III also evaluated possible differences between patients in baseline remission or baseline LDA and did not find evidence to support a statistically significant impact on achieving the co-primary endpoints or successful biologic tapering, respectively. However, caution must be applied when interpreting the sub-group analyses as these analyses not are adequately powered. Nonetheless, the

evidence raises the question: does patients with IA need to be in sustained remission before tapering is initiated, as required in the current international guidelines (23–25), or is sustained LDA sufficient? Future research is needed to explore the impact of baseline disease activity for achieving successful biologic tapering further.

In study II, switch to another biological therapy due to loss of therapeutic response (persistent flare) was not more frequent in the tapering group (1% [1/95]) compared to the continuation group (6% [3/47]). Similarly, only few patients had persistent flare and needed to be switched to another biological drug in previous disease activity-guided tapering trials: the STRASS trial (tapering 3 % [2/64] vs continuation 0% [0/73]) (79), the DRESS trial (tapering 3% [4/121 vs continuation 7% [4/59]) (76), the ADOPT trial (4% [5/141]) (133), and the DOBIS trial (2% [2/106]) (132).

The evidence for disease activity-guided tapering of biologics in patients with PsA is limited to study II and the recent TAPAS trial (151). TAPAS was a retrospective cohort study conducted in an outpatient setting with a study population of PsA and axSpA. Three different time periods were explored: 1) Initial TNFi full dose period, 2) TNFi disease activity-guided tapering period and, 3) Stable TNFi dose period after tapering. In total, 153 patients with PsA and 171 patients with axSpA were included with 46 and 44 months follow-up, respectively. Disease activity remained stable with no statistically significant difference between the time periods for neither PsA nor axSpA; thus, the finding is comparable to other trials evaluating disease activity-guided tapering of biologics (76,97,132,133), except the STRASS trial (79), as discussed previously. TNF dose reduction by one-third was possible across the two diagnoses (151). Thus, lower than reported in other disease activity-guided tapering trials (76,97,132,133). The study authors lists suboptimal execution of the local tapering protocol as the most likely explanation for this difference.

Recently, Ye et al. conducted a retrospective observational study in patients with AS who tapered their etanercept biosimilar guided after disease activity in a real-world outpatient setting (150). Data on 108 patients with AS with ≥1 year follow-up were analysed. Almost all patients (98% [106/108]) gradually spaced the etanercept dosing interval. Between month 6 and 12, the mean dosing interval was 10.49 ±0.39 days; thus, considerably higher than the standard 3.5 (for the 25 mg dose). Thus, more patients managed to reach a considerable dose reduction than reported in previous disease activity-guided tapering trials (76,79,97,132,133,151). Disease activity remained stable despite tapering to a lower dose (150) comparable to previous trials (76,97,132,133,151). Similar to study II, 11% (12/108) of patients with AS managed to withdraw their etanercept biosimilar without experiencing a flare (150).

The TARA study evaluated disease activity-guided tapering of TNFi versus conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in

patients with RA in sustained remission (152). At 12 months follow-up, there was a significant difference in tapering status as patients in the csDMARD group were able to taper more aggressively than the TNFi group. Thus, 90% (77/85) vs 82% (73/89) were able to taper their csDMARDs or TNFi, respectively, of which 68% (58/85) vs 51% (45/89) completely withdrew the treatment. Thus, the proportion of patients able to discontinue TNFi were larger than in previous disease activity-guided tapering trials (76,79,97,132,133,150). Yet, disease activity was similar between the two groups at month 12 (152); comparable to findings in the majority of disease-activity guided tapering trials (76,97,132,133,150,151). At 2 years follow-up, drug free remission (i.e., withdrawal of TNFi and csDMARDs) was managed by 20% (19/94) in the csDMARD group and 11% (10/95) in the TNFi group while comparable disease activity was maintained (144). Interestingly, the expenses for the two tapering strategies were similar at 2 years follow-up as the savings in the TNFi group due to lower medication costs was balanced out by indirect expenses due to patient productivity loss (at work) (153). Thus, the potential economic benefits for tapering biologics first might not be as large as expected; especially in recent years as biosimilars have reduced the costs considerably. The observed increase in patient productivity loss is noteworthy and future research is needed to explore this further. However, other possible benefits or harms to tapering biologics vs csDMARDs first should also be considered. An argument for tapering biologics first could be safety as patients with RA or PsA treated with biologics compared to csDMARDs have been shown to have an increased risk for serious infections (32,154,155). Another argument could be immunogenicity as presence of anti-drug antibodies (ADAb) against TNFis have been reported to be more frequent in patients with IA who received low dose or no MTX (156–161). Thus, tapering csDMARDs, such as MTX, first could increase the risk of developing ADAb which could lead to loss of the TNFi therapeutic response. These concerns have also been raised for tapering biologics first i.e., that lowering the biologic dose or prolonging the biologic dosing interval could lead to development of ADAb; thereby, risking loss of the therapeutic response. However, the DRESS trial and the STRASS trial did not find presence of ADAb to be predictive of flare or achieving successful TNFi tapering or withdrawal in patients with RA (162,163). Thus, future studies are needed to explore these aspects to tapering biologics vs csDMARDs first in patients with IA.

4.4. SAFETY, BENEFIT, AND HARM

In study II, the frequency of adverse events (AEs) and serious adverse events (SAEs) were comparable between the tapering group and the continuation group. Similarly, no significant difference in safety measures was observed when comparing biologic withdrawal or biologic tapering to biologic continuation in Study I. Recent meta-analyses based on observational studies and/or RCTs with a RA or axSpA population comparing biologic tapering to biologic continuation also

reported no safety concerns (141,164). Thus, when considering the safety evidence no increased risk of harms are seen when comparing biologic dose reduction to biologic continuation but just as important no apparent safety benefits e.g. lower risk of infection or adverse events are observed despite a lower biologic dose. However, successful biologic tapering could enhance patient satisfaction and health-related quality of life when fewer drug doses are needed to control the disease (131) as the patient becomes less dependent of their biological therapy e.g. fewer visits to the outpatient clinic for intravenous infusions or for medicine pickup.

As previously discussed, a considerable risk for flare have been reported when biological therapies are tapered but reassuringly only few patients lose the therapeutic response and need to be switched to another biological drug. Thus, flares are generally managed well with biologic dose escalation and/or other rescue therapies such as glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs).

4.5. PREDICTING SUCCCESSFUL BIOLOGIC TAPERING

In recent years, efforts have been put into identifying possible predictors for successful biologic tapering as this would provide a better insight into which patients to taper and just as important which not to taper due to an excessive flare risk. Study I evaluated predictors for successful tapering and for flare from the included RCTs and found large heterogeneity in the reported predictors; thus, no consistent predictors were identified in RA or axSpA. Based on data from RCTs and observational studies, higher adalimumab serum through level was the only identified predictor for successful biologic tapering among patients with RA in a systematic review by Tweehuysen et al (102). However, caution must be applied when considering the results, as the certainty of the evidence for the predictor was considered to be low. Just recently, van der Leeuw et al. developed and validated the first dynamic model to predict the risk of flare within three months during biologic tapering in patients with RA (165). The model was based on longitudinal data from routine care and contained the variables: two latent DAS28-trajectories, biologic type and dose, disease duration, and positivity for rheumatoid factor and/or anti-citrullinated peptide antibody. External validation of the model was performed with data from the DRESS trial. Using the prediction model to facilitate treatment changes during biologic tapering was superior to both the disease activity-guided tapering strategy in the DRESS trial and the tapering strategy in routine care. Thus, simulation showed that the model significantly reduced the mean number of flares from 1.21 (95% CI: 0.99 to 1.43) in the DRESS study to 0.75 (95% CI: 0.54 to 0.96) with the prediction model. As the tapering strategy in routine care was less aggressive, the mean number of flares was lower 0.48 (95% CI: 0.24 to 0.72). However, the prediction model managed to maintain a considerable biologic dose

reduction as the mean biologic dose was 64% (95% CI: 61% to 68%) of standard dose compared to 54% (95% CI: 50% to 58%) in the DRESS trial and 91% (95% CI: 86% to 96%) in routine care. Future research is needed to test the model in other data sets; however, the model could be a pivotal new tool to guide physicians and patients with RA during biologic tapering.

Study III evaluated potential predictors for successful biologic tapering across IA diagnoses based on data from the BIODOPT trial. However, the study has a potential risk of type II error i.e. failure to identify relevant predictors due to the reduced statistical power as the target population in study II not was reached. Nonetheless, better baseline mental health (higher SF-36 MCS) was observed to be a potentially important non-significant predictor for achieving successful biologic tapering. Similarly, the OPTTIRA trial found mental health to be of considerable importance during TNFi tapering among patients with RA as a lower SF-36 mental health subscale significantly increased the risk of flare (166). Thus, assessment of mental health before initiating biologic tapering could be important as patients with better mental health at baseline may achieve successful tapering more frequently than patients with worse mental health. However, as these findings only is reported in two tapering trials caution must be applied. The low statistical power in study III also made it difficult to include disease specific baseline variables (e.g. DAS28-CRP or ASDAS) in the prediction models. Thus, future research, especially with larger data sets, is needed to provide additional insight into possible predictors for successful biologic tapering across IA diagnoses.

CHAPTER 5. CONCLUSION AND FUTURE PERSPECTIVES

This dissertation proved a highly increased risk for flare and persistent flare when biologic withdrawal was compared to biologic continuation in patients with RA or axSpA based on data from RCTs whereas biologic tapering only had a significantly increased risk for flare and not for persistent flare. We conducted a RCT to evaluate disease activity-guided tapering of biologics in patients with IA to continuation of biologics as usual care. The disease activity-guided tapering algorithm for biologics was found to be effective and safe as a considerable dose reduction could be achieved while equivalent disease activity was maintained. Better baseline mental health status was identified as a potentially important nonsignificant predictor for achieving successful biologic tapering. Conclusions for the individual studies are summarised in greater details below.

5.1. STUDY I

The following conclusions for patients with RA or axSpA (no studies with a PsA population) can be drawn from study I:

- Biologic withdrawal vs biologic continuation proved to have a highly increased risk for flare and persistent flare.
- Biologic withdrawal vs biologic tapering was observed to have a highly increased odds for flare and persistent flare.
- Biologic tapering vs biologic continuation only demonstrated a significantly increased risk for flare and not for persistent flare.
- Safety measures were comparable across the different groups.
- Based on the available evidence from RCTs, biologic tapering seem to be a more favourable dose reduction strategy than biologic withdrawal.

5.2. STUDY II

The following conclusions for patients with IA in sustained LDA on biologics can be drawn from study II:

- Significantly more patients in the tapering group than in the continuation group managed to reduce their biologic dose by ≥50% at 18 months.
- Equivalent disease activity between the tapering group and the continuation group was demonstrated at 18 months.

- The tapering group experienced flares more frequent but rescue therapy managed the flares as no increased risk of persistent flare was observed.
- The frequency of AEs and SAEs was comparable between the trial groups.
- Disease activity-guided tapering of biologics is judged to be an effective and safe instrument to reduce the biologic dose.

5.3. STUDY III

The following conclusions for patients with IA in sustained LDA on biologics can be drawn from study III:

- Two thirds of patients in the tapering group managed to reduce their biologic dose while maintaining LDA at 18 months.
- One third of patients in the tapering group achieved successful biologic tapering i.e., ≥50% biologic dose reduction while maintaining LDA.
- The only independent predictor for reaching successful biologic tapering was allocation to the tapering group.
- Better baseline mental health status was identified as a potentially important nonsignificant predictor for reaching successful biologic tapering.

5.4. FUTURE PERSPECTIVES

The three studies presented in this dissertation were conducted to provide additional knowledge on dose reduction of biologics in patients with IA in sustained remission or LDA. Future RCTs are needed to provide additional evidence across IA diagnoses, across biological drugs, and across different dose reduction strategies i.e., fixed dose reduction versus disease activity-guided tapering. Identification of possible predictors for successful biologic tapering in patients with IA is needed to guide the decision between the patient and the physician. Furthermore, additional evidence on several aspects of biologic tapering in patients with IA is still needed and it would be interesting to:

- Evaluate long-term follow-up after biologic tapering as studies with >12 months follow-up are limited.
- Assess the economic aspects of biologic tapering versus biologic continuation (healthcare costs, quality-adjusted life-year etc.) in light of the recent lower biologic costs due to biosimilars.
- Identify possible blood sample biomarkers for achieving successful biologic tapering to guide the decision of initiating tapering.

LITERATURE

1. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res. 2015;67:891–7.

2. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.

3. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classifi cation criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580–8.

4. Moll J, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3:55–78.

5. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665–73.

6. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777–83.

7. Van der Linden S, Valkenburg HA, Cats A. Evaluation of Diagnostic Criteria for Ankylosing Spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361–8.

8. Sampaio-Barros PD, Bertolo MB, Kraemer MH, et al. Primary ankylosing spondylitis: Patterns of disease in a Brazilian population of 147 patients. J Rheumatol. 2001;28:560–5.

9. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet. 2017;390:73–84.

10. Rusman T, van Bentum RE, van der Horst-Bruinsma IE. Sex and gender differences in axial spondyloarthritis: Myths and truths. Rheumatology (Oxford). 2020;59:S38–46.

11. Feldtkeller E, Khan MA, van der Heijde D, et al. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int. 2003;23:61–6.

12. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. N Engl J Med. 2017;376:957–70.

13.   Pittam B, Gupta S, Harrison NL, et al. Prevalence of extra-articular manifestations in psoriatic arthritis: A systematic review and meta-analysis. Rheumatology (Oxford). 2020;59:2199–206.

14.   Egeberg A, Kristensen LE, Thyssen JP, et al. Incidence and prevalence of psoriatic arthritis in Denmark: a nationwide register linkage study. Ann Rheum Dis. 2017;76:1591–7.

15.   Alinaghi F, Calov M, Kristensen LE, et al. Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies. J Am Acad Dermatol. 2019;80:251–65.

16.   Menter A. Psoriasis and psoriatic arthritis overview. Am J Manaf Care. 2016;22:S216-S224.

17.   Lee D, Weinblatt M. Rheumatoid Arthritis. Lancet. 2001;358:903–11.

18.   Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet. 2010;376:1094–108.

19.   Sieper J, Braun J, Dougados M, et al. Axial spondyloarthritis. Nat Rev Dis Prim. 2015;1:15013.

20.   McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205–19.

21.   Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet. 2018;391:2273–84.

22.   Schett G, Lories RJ, D'Agostino MA, et al. Enthesitis: From pathophysiology to treatment. Nat Rev Rheumatol. 2017;13:731–41.

23.   Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685–99.

24.   Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020;79:700–12.

25.   Van Der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76:978–91.

26. Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis. 2018;77:3–17.

27. Takeuchi T. Revolutionary change in rheumatoid arthritis management with biological therapy. Keio J Med. 2011;60:75–81.

28. Cruz-Machado AR, Rodrigues-Manica S, Silva JL, et al. Effect of biologic disease-modifying anti-rheumatic drugs targeting remission in axial spondyloarthritis: Systematic review and meta-analysis. Reumatology (Oxford). 2020;59:3158–71.

29. Mysler E, Caubet M, Lizarraga A. Current and emerging DMARDs for the treatment of rheumatoid arthritis. Open Access Rheumatol. 2021;13:139–52.

30. Rossi D, Modena V, Sciascia S, et al. Rheumatoid arthritis: Biological therapy other than anti-TNF. Int Immunopharmacol. 2015;27:185–8.

31. Singh J, Hossain A, Tanjong Ghogomu E, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network metaanalysis. Cochrane Database Syst Rev. 2016;5:CD012183.

32. Kerschbaumer A, Smolen JS, Dougados M, et al. Pharmacological treatment of psoriatic arthritis: A systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2020;79:778–86.

33. Thorsen H, Hansen TM, McKenna SP, et al. Adaptation into Danish of the Stanford Health Assessment Questionnaire (HAQ) and the Rheumatoid Arthritis Quality of Life Scale (RAQoL). Scand J Rheumatol. 2001;30:103–9.

34. Linde L, Sørensen J, Østergaard M, et al. Health-related quality of life: Validity reliability, and responsiveness of SF-36, EQ-15D, EQ-5D, RAQoL, and HAQ in patients with rheumatoid arthritis. J Rheumatol. 2008;35:1528–37.

35. Wan MT, Walsh JA, Craig ET, et al. A comparison of physical function instruments in psoriatic arthritis: HAQ-DI vs MDHAQ vs PROMIS10 global physical health. Rheumatology (Oxford). 2021;60:2307–16.

36. Ward M, Kuzis S. Validity and sensitivity to change of spondylitis-specific

measures of functional disability. J Rheumatol. 1999;26:121–7.

37.   Højgaard P, Klokker L, Orbai AM, et al. A systematic review of measurement properties of patient reported outcome measures in psoriatic arthritis: A GRAPPA-OMERACT initiative. Semin Arthritis Rheum. 2018;47:654–65.

38.   Gossec L, Portier A, Landewé R, et al. Preliminary definitions of "flare" in axial spondyloarthritis, based on pain, BASDAI and ASDAS-CRP: An ASAS initiative. Ann Rheum Dis. 2016;75:991–6.

39.   Van Tubergen A, Black PM, Coteur G. Are patient-reported outcome instruments for ankylosing spondylitis fit for purpose for the axial spondyloarthritis patient? A qualitative and psychometric analysis. Rheumatology (Oxford). 2015;54:1842–51.

40.   Nikiphorou E, Radner H, Chatzidionysiou K, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: A review of the literature. Arthritis Res Ther. 2016;18:251.

41.   Cauli A, Gladman DD, Mathieu A, et al. Patient global assessment in psoriatic arthritis: A multicenter GRAPPA and OMERACT study. J Rheumatol. 2011;38:898–903.

42.   Pedersen OB, Hansen GO, Svendsen AJ, et al. Adaptation of the Bath measures on disease activity and function in ankylosing spondylitis into Danish. Scand J Rheumatol. 2007;36:22–7.

43.   Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum. 2000;43:1478–87.

44.   Husted JA, Gladman DD, Farewell VT, et al. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. J Rheumatol. 1997;24:511–7.

45.   Scott DL, Houssien DA. Joint assessment in rheumatoid arthritis. Br J Rheumatol. 1996;35:S14–S18.

46.   Duarte-García A, Leung YY, Coates LC, et al. Endorsement of the 66/68 Joint Count for the Measurement of Musculoskeletal Disease Activity: OMERACT 2018 Psoriatic Arthritis Workshop Report. J Rheumatol. 2019;46:996–1005.

47.   De Winter JJ, Paramarta JE, de Jong HM, et al. Peripheral disease contributes

significantly to the level of disease activity in axial spondyloarthritis. RMD Open. 2019;5:e000802.

48. Kristensen S, Christensen JH, Schmidt EB, et al. Assessment of enthesitis in patients with psoriatic arthritis using clinical examination and ultrasound. Muscles Ligaments Tendons J. 2016;6:241–7.

49. Maksymowych WP, Mallon C, Morrow S, et al. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. Ann Rheum Dis. 2009;68:948–53.

50. Ogdie A, Coates LC, Mease P. Measuring Outcomes in Psoriatic Arthritis. Arthritis Care Res. 2020;72:S82–109.

51. Ogdie A, Duarte-García A, Hwang M, et al. Measuring Outcomes in Axial Spondyloarthritis. Arthritis Care Res. 2020;72:S47–71.

52. Coates LC, Helliwell PS. Disease measurement - Enthesitis, skin, nails, spine and dactylitis. Best Pract Res Clin Rheumatol. 2010;24:659–70.

53. Cassell SE, Bieber JD, Rich P, et al. The Modified Nail Psoriasis Severity Index : validation of an Instrument to Assess Psoriatic Nail Involvement in Patients with Psoriatic Arthritis. J Rheumatol. 2007;34:123–9.

54. Jenkinson T, Mallorie PA, Whitelock HC, et al. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol. 1994;21:1694–8.

55. Keeling SO, Landewé R, van der Heijde D, et al. Testing of the preliminary OMERACT validation criteria for a biomarker to be regarded as reflecting structural damage endpoints in rheumatoid arthritis clinical trials: The example of C-reactive protein. J Rheumatol. 2007;34:623–33.

56. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68:954–60.

57. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of Rheumatoid Arthritis Disease Activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score

(PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). Arthritis Care Res. 2011;63:S14–36.

58. Inoue E, Yamanaka H, Hara M, et al. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis. 2007;66:407–9.

59. Fleischmann R, van der Heijde D, Koenig AS, et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? Ann Rheum Dis. 2015;74:1132–7.

60. Fleischmann RM, van der Heijde D, Gardiner PV, et al. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD Open. 2017;3:e000382.

61. Hensor EMA, Emery P, Bingham SJ, et al. Discrepancies in categorizing rheumatoid arthritis patients by DAS-28(ESR) and DAS-28(CRP): Can they be reduced? Rheumatology (Oxford). 2010;49:1521–9.

62. Van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:1811–8.

63. Machado P, Landewé R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): Defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis. 2011;70:47–53.

64. Machado PM, Landewé R, van der Heijde D. Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis. 2018;77:1539–40.

65. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Rheumatol. 2019;71:5–32.

66. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol.

2016;68:1060–71.

67. Schoels M, Aletaha D, Funovits J, et al. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis. 2010;69:1441–7.

68. Schoels MM, Aletaha D, Alasti F, et al. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. Ann Rheum Dis. 2016;75:811–8.

69. Bartlett SJ, Hewlett S, Bingham 3rd CO, et al. Identifying core domains to assess flare in rheumatoid arthritis: an OMERACT international patient and provider combined Delphi consensus. Ann Rheum Dis. 2012;71:1855–60.

70. Van der Maas A, Lie E, Christensen R, et al. Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. Ann Rheum Dis. 2013;72:1800–5.

71. Molto A, Gossec L, Meghnathi B, et al. An assessment in spondyloarthritis international society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. Ann Rheum Dis. 2018;77:124–7.

72. Verhoef LM, Bos DPG, van den Ende CHM, et al. Cost-effectiveness of five different anti-tumour necrosis factor tapering strategies in rheumatoid arthritis: a modelling study. Scand J Rheumatol. 2019;48:439–47.

73. Meyer MK, Andersen M, Ring T, et al. Personalized rheumatic medicine through dose reduction reduces the cost of biological treatment–a retrospective intervention analysis. Scand J Rheumatol. 2019;48:398–407.

74. Murphy CL, Awan S, Sullivan MO, et al. Major cost savings associated with dose reduction in patients with inflammatory arthritis. Ir Med J. 2015;108:19–21.

75. Van Herwaarden N, den Broeder AA, Jacobs W, et al. Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. Cochrane Database Syst Rev. 2014;9:CD010455.

76. Van Herwaarden N, van der Maas A, Minten MJM, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. BMJ. 2015;350:h1389.

77.   L'ami MJ, Krieckaert CLM, Nurmohamed MT, et al. Successful reduction of overexposure in patients with rheumatoid arthritis with high serum adalimumab concentrations: An open-label, non-inferiority, randomised clinical trial. Ann Rheum Dis. 2018;77:484–7.

78.   Yates M, Hamilton LE, Elender F, et al. Is etanercept 25 mg once weekly as effective as 50 mg at maintaining response in patients with ankylosing spondylitis? A randomized control trial. J Rheumatol. 2015;42:1177–85.

79.   Fautrel B, Pham T, Alfaiate T, et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). Ann Rheum Dis. 2016;75:59–67.

80.   Cantini F, Niccoli L, Cassarà E, et al. Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: a long-term follow-up study. Biologics. 2012;6:201–6.

81.   Lesuis N, Verhoef LM, Nieboer LM, et al. Implementation of protocolized tight control and biological dose optimization in daily clinical practice: results of a pilot study. Scand J Rheumatol. 2017;46:152-155.

82.   Brocq O, Millasseau E, Albert C, et al. Effect of discontinuing TNFα antagonist therapy in patients with remission of rheumatoid arthritis. Jt Bone Spine. 2009;76:350–5.

83.   Tanaka Y, Takeuchi T, Mimori T, et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. Ann Rheum Dis. 2010;69:1286–91.

84.   Van den Broek M, Klarenbeek NB, Dirven L, et al. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. Ann Rheum Dis. 2011;70:1389–94.

85.   Nishimoto N, Amano K, Hirabayashi Y, et al. Drug free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy (DREAM) study. Mod Rheumatol. 2014;24:17–25.

86.   Takeuchi T, Matsubara T, Ohta S, et al. Biologic-free remission of established rheumatoid arthritis after discontinuation of abatacept: a prospective, multicentre, observational study in Japan. Rheumatology (Oxford).

2015;54:683–91.

87.   Tanaka Y, Hirata S, Kubo S, et al. Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. Ann Rheum Dis. 2015;74:389–95.

88.   Van der Maas A, Kievit W, van den Bemt BJF, et al. Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. Ann Rheum Dis. 2012;71:1849–54.

89.   Emery P, Hammoudeh M, FitzGerald O, et al. Sustained Remission with Etanercept Tapering in Early Rheumatoid Arthritis. N Engl J Med. 2014;371:1781–92.

90.   Kikuchi J, Kondo T, Shibata A, et al. Efficacy and tolerability of six-week extended dosing interval with tocilizumab therapy in a prospective cohort as remission maintenance in patients with rheumatoid arthritis. Mod Rheumatol. 2018;28:444–51.

91.   Yasuda S, Ohmura K, Kanazawa H, et al. Maintenance treatment using abatacept with dose reduction after achievement of low disease activity in patients with rheumatoid arthritis (MATADOR)–A prospective, multicenter, single arm pilot clinical trial. Mod Rheumatol. 2017;27:930–7.

92.   Baraliakos X, Listing J, Rudwaleit M, et al. Safety and efficacy of readministration of infliximab after longterm continuous therapy and withdrawal in patients with ankylosing spondylitis. J Rheumatol. 2007;34:510–5.

93.   Song I-H, Althoff CE, Haibel H, et al. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. Ann Rheum Dis. 2012;71:1212–5.

94.   Haibel H, Heldmann F, Braun J, et al. Long-term efficacy of adalimumab after drug withdrawal and retreatment in patients with active non-radiographically evident axial spondyloarthritis who experience a flare. Arthritis Rheum. 2013;65:2211–3.

95.   Mörck B, Pullerits R, Geijer M, et al. Infliximab dose reduction sustains the clinical treatment effect in active HLAB27 positive ankylosing spondylitis: A two-year pilot study. Mediators Inflamm. 2013;2013:289845.

96. Almirall M, Salman-Monte TC, Lisbona MP, et al. Dose reduction of biological treatment in patients with axial spondyloarthritis in clinical remission: Are there any differences between patients who relapsed and to those who remained in low disease activity? Rheumatol Int. 2015;35:1565–8.

97. Arends S, van der Veer E, Kamps FBS, et al. Patient-tailored dose reduction of TNF-α blocking agents in ankylosing spondylitis patients with stable low disease activity in daily clinical practice. Clin Exp Rheumatol. 2015;33:174–80.

98. Závada J, Uher M, Sisol K, et al. A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: a propensity score-matched cohort study. Ann Rheum Dis. 2016;75:96–102.

99. Araujo EG, Finzel S, Englbrecht M, et al. High incidence of disease recurrence after discontinuation of disease-modifying antirheumatic drug treatment in patients with psoriatic arthritis in remission. Ann Rheum Dis. 2015;74:655–60.

100. De Stefano R, Frati E, de Quattro D, et al. Low Doses of Etanercept Can Be Effective to Maintain Remission in Psoriatic Arthritis Patients. J Clin Rheumatol. 2018;24:127–31.

101. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. BMJ. 2014;350:g7594.

102. Tweehuysen L, van den Ende CH, Beeren FMM, et al. Little Evidence for Usefulness of Biomarkers for Predicting Successful Dose Reduction or Discontinuation of a Biologic Agent in Rheumatoid Arthritis: A Systematic Review. Arthritis Rheumatol. 2017;69:301–8.

103. Verhoef LM, van den Bemt B, van der Maas A, et al. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. Cochrane Database Syst Rev. 2019;5:CD010455.

104. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869.

105. Gøtzsche PC. Lessons from and cautions about noninferiority and equivalence randomized trials. JAMA. 2006;295:1172–4.

106. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA. 2012;308:2594–604.

107. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.0 (updated July 2019). Cochrane; 2021. Available from: Available from www.training.cochrane.org/handbook.

108. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. BMJ. 2009;339:b2700.

109. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing Summary of Findings tables - Binary outcomes. J Clin Epidemiol. 2013;66:158–72.

110. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: A comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007;26:53–77.

111. Cipriani A, Higgins JPT, Geddes JR,et al. Conceptual and Technical Challenges in Network Meta-analysis. Ann Intern Med. 2013;159:130–7.

112. Ibrahim F, Lorente-Cánovas B, Doré CJ, et al. Optimizing treatment with tumour necrosis factor inhibitors in rheumatoid arthritis-A proof of principle and exploratory trial: Is dose tapering practical in good responders? Rheumatology (Oxford). 2017;56:2004–14.

113. Weinblatt ME, Bingham 3rd CO, Burmester GR, et al. A Phase III Study Evaluating Continuation, Tapering, and Withdrawal of Certolizumab Pegol After One Year of Therapy in Patients With Early Rheumatoid Arthritis. Arthritis Rheumatol. 2017;69:1937–48.

114. Gratacós J, Pontes C, Juanola X, et al. Non-inferiority of dose reduction versus standard dosing of TNF-inhibitors in axial spondyloarthritis. Arthritis Res Ther. 2019;21:11.

115. Cantini F, Niccoli L, Cassará E, et al. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis : a randomized, prospective, long-term, follow-up study. Biologics. 2013;7:1–6.

116. Van Vollenhoven RF, Østergaard M, Leirisalo-Repo M, et al. Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. Ann Rheum Dis. 2016;75:52–8.

117.   Smolen JS, Nash P, Durez P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): A randomised controlled trial. Lancet. 2013;381:918–29.

118.   Landewé RBM, van der Heijde D, Dougados M, et al. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. Ann Rheum Dis. 2020;79:920–8.

119.   Sanmarti R, Veale DJ, Martin-Mola E, et al. Reducing or Maintaining the Dose of Subcutaneous Tocilizumab in Patients With Rheumatoid Arthritis in Clinical Remission: A Randomized, Open-Label Trial. Arthritis Rheumatol. 2019;71:1616–25.

120.   Verhoef LM, den Broeder N, Thurlings RM, et al. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. Lancet Rheumatol. 2019;1:e145–53.

121.   Westhovens R, Robles M, Ximenes AC, et al. Maintenance of remission following 2 years of standard treatment then dose reduction with abatacept in patients with early rheumatoid arthritis and poor prognosis. Ann Rheum Dis. 2015;74:564–8.

122.   Takeuchi T, Genovese MC, Haraoui B, et al. Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: Results of a prospective study. Ann Rheum Dis. 2019;78:171–8.

123.   Chatzidionysiou K, Turesson C, Teleman A, et al. A multicentre, randomised, controlled, open-label pilot study on the feasibility of discontinuation of adalimumab in established patients with rheumatoid arthritis in stable clinical remission. RMD Open. 2016;2:e000133.

124.   Curtis JR, Emery P, Karis E, et al. Etanercept or Methotrexate Withdrawal in Rheumatoid Arthritis Patients in Sustained Remission. Arthritis Rheumatol. 2021;73:759–68.

125.   Pavelka K, Akkoç N, Al-Maini M, et al. Maintenance of remission with combination etanercept–DMARD therapy versus DMARDs alone in active rheumatoid arthritis: results of an international treat-to-target study conducted in regions with limited biologic access. Rheumatol Int. 2017;37:1469–79.

126.   Yamanaka H, Nagaoka S, Lee SK, et al. Discontinuation of etanercept after achievement of sustained remission in patients with rheumatoid arthritis who

initially had moderate disease activity - results from the ENCOURAGE study, a prospective, international, multicenter randomized study. Mod Rheumatol. 2016;26:651–61.

127. Ghiti Moghadam M, Vonkeman HE, Ten Klooster PM, et al. Stopping Tumor Necrosis Factor inhibitor Treatment in Patients with Established Rheumatoid Arthritis in Remission or with Stable Low Disease Activity: A Pragmatic Randomized Multicenter Open-Label Controlled Trial. Arthritis Rheumatol. 2016;68:1810–7.

128. Landewé R, Sieper J, Mease P, Mease P, et al. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet. 2018;392:134–44.

129. Smolen JS, Emery P, Fleischmann R, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: The randomised controlled OPTIMA trial. Lancet. 2014;383:321–32.

130. Anglemyer A, Horvath H, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev. 2014:MR000034.

131.   Richter A, Anton SF, Koch P, et al. The impact of reducing dose frequency on health outcomes. Clin Ther. 2003;25:2307–35.

132. Wetterslev M, Georgiadis S, Sørensen IJ, et al. Tapering of TNF inhibitors in axial spondyloarthritis in routine care - 2-year clinical and MRI outcomes and predictors of successful tapering. Rheumatology (Oxford). 2021;keab755.

133. Brahe CH, Krabbe S, Østergaard M, et al. Dose tapering and discontinuation of biological therapy in rheumatoid arthritis patients in routine care - 2-year outcomes and predictors. Rheumatology (Oxford). 2019;58(1):110–9.

134. Boers N, Michielsens CAJ, van der Heijde D, et al. The effect of tumour necrosis factor inhibitors on radiographic progression in axial spondyloarthritis: A systematic literature review. Rheumatology (Oxford). 2019;58:1907–22.

135. Moons KGM, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. Ann Intern Med. 2015;162:W1–73.

136.   Henaux S, Ruyssen-Witrand A, Cantagrel A, et al. Risk of losing remission, low disease activity or radiographic progression in case of bDMARD discontinuation or tapering in rheumatoid arthritis: systematic analysis of the literature and meta-analysis. Ann Rheum Dis. 2018;77:515–22.

137.   Vasconcelos LB, Silva MT, Galvao TF. Reduction of biologics in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatol Int. 2020;40:1949–59.

138.   Verhoef LM, Tweehuysen L, Hulscher ME, et al. bDMARD Dose Reduction in Rheumatoid Arthritis: A Narrative Review with Systematic Literature Search. Rheumatol Ther. 2017;4:1–24.

139.   Schlager L, Loiskandl M, Aletaha D, et al. Predictors of successful discontinuation of biologic and targeted synthetic DMARDs in patients with rheumatoid arthritis in remission or low disease activity: A systematic literature review. Rheumatology (Oxford). 2020;59:324–34.

140.   Navarro-Compán V, Plasencia-Rodríguez C, de Miguel E, et al. Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: A systematic literature review. Rheumatology (Oxford). 2016;55:1188–94.

141.   Lawson DO, Eraso M, Mbuagbaw L, et al. Tumor Necrosis Factor Inhibitor Dose Reduction for Axial Spondyloarthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Arthritis Care Res. 2021;73:861–72.

142.   Pavy S, Brophy S, Calin A. Establishment of the minimum clinically important difference for the bath ankylosing spondylitis indices: A prospective study. J Rheumatol. 2005;32:80–5.

143.   Ye W, Tucker LJ, Coates LC. Tapering and Discontinuation of Biologics in Patients with Psoriatic Arthritis with Low Disease Activity. Drugs. 2018;78:1705–15.

144.   Van Mulligen E, Weel AE, Hazes JM, et al.. Tapering towards DMARD-free remission in established rheumatoid arthritis: 2-year results of the TARA trial. Ann Rheum Dis. 2020;79:1174–81.

145.   Lillegraven S, Sundlisæter NP, Aga AB, et al. Stable Versus Tapered and Withdrawn Treatment With Tumor Necrosis Factor Inhibitor in Rheumatoid Arthritis Remission (Arctic Rewind): a Randomised, Open-Label, Phase 4, Non-Inferiority Trial. Arthritis Rheumatol. 2020;72:S10.

146. Lillegraven S, Sundlisæter NP, Aga AB, et al. Stable versus Tapered and Withdrawn Treatment with Tumor Necrosis Factor Inhibitor in Rheumatoid Arthritis Remission: A Randomized, Open-Label, Phase 4, Non-Inferiority Trial. Ann Rheum Dis. 2020;79:S14–5.

147. Emery P, Burmester GR, Naredo E, et al. Adalimumab dose tapering in patients with rheumatoid arthritis who are in long-standing clinical remission: Results of the phase IV PREDICTRA study. Ann Rheum Dis. 2020;79:1023–30.

148. Landewé RBM, Gensler LS, Poddubnyy D, et al. Continuing versus withdrawing ixekizumab treatment in patients with axial spondyloarthritis who achieved remission: Efficacy and safety results from a placebo-controlled, randomised withdrawal study (COAST-Y). Ann Rheum Dis. 2021;80:1022–30.

149. Zhang T, Zhu J, He D, et al. Disease activity guided stepwise tapering or discontinuation of rhTNFR:Fc, an etanercept biosimilar, in patients with ankylosing spondylitis: a prospective, randomized, open-label, multicentric study. Ther Adv Musculoskelet Dis. 2020;12:1759720X20929441.

150. Ye L, Zhou L, Bian J, et al. Disease Activity-Guided Stepwise Tapering but Not Discontinuation of Biologics Is a Feasible Therapeutic Strategy for Patients with Ankylosing Spondylitis: Real-World Evidence. Adv Ther. 2022;39:1393–402.

151. Michielsens CAJ, den Broeder N, Mulder MLM, et al. Tumour necrosis factor inhibitor dose adaptation in psoriatic arthritis and axial spondyloarthritis (TAPAS): a retrospective cohort study. Rheumatology (Oxford). 2021;keab741.

152. Van Mulligen E, de Jong PHP, Kuijper TM, et al. Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: First-year results of the randomised controlled TARA study. Ann Rheum Dis. 2019;78:746–53.

153. Van Mulligen E, Weel AE, Kuijper TM, et al. Two-year cost effectiveness between two gradual tapering strategies in rheumatoid arthritis: Cost-utility analysis of the TARA trial. Ann Rheum Dis. 2020;79:1550–6.

154. Ramiro S, Sepriano A, Chatzidionysiou K, et al. Safety of synthetic and biological DMARDs: A systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2017;76:1101–136.

155. Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: A systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020;79:760–70.

156. Jani M, Barton A, Warren RB, et al. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford). 2014;53:213–22.

157. Jani M, Chinoy H, Warren RB, et al. Clinical utility of random anti-tumor necrosis factor drug-level testing and measurement of antidrug antibodies on the long-term treatment response in rheumatoid arthritis. Arthritis Rheumatol. 2015;67:2011–9.

158. Chen DY, Chen YM, Tsai WC, et al. Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. Ann Rheum Dis. 2015;74:e16.

159. Hiltunen J, Parmanne P, Sokka T, et al. Immunogenicity of subcutaneous TNF inhibitors and its clinical significance in real-life setting in patients with spondyloarthritis. Rheumatol Int. 2021;doi: 10.1007/s00296-021-04955-8.

160. Husni ME, Deodhar A, Schwartzman S, et al. Pooled safety results across phase 3 randomized trials of intravenous golimumab in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Arthritis Res Ther. 2022;24:73.

161. Hoxha A, Calligaro A, Tonello M, et al. The clinical relevance of early anti-adalimumab antibodies detection in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: A prospective multicentre study. Jt Bone Spine. 2016;83:167–71.

162. Bouman C, van Herwaarden N, van den Hoogen FHJ, et al. Prediction of successful dose reduction or discontinuation of adalimumab, etanercept, or infliximab in rheumatoid arthritis patients using serum drug levels and antidrug antibody measurement. Expert Opin Drug Metab Toxicol. 2017;13:597–603.

163. Marotte H, Rinaudo M, Paul S, et al. No Prediction of Relapse by TNF Blocker Concentrations or Detection of Antibodies against anti-TNF: Data from Strass Study. Ann Rheum Dis. 2016;75:S495.

164. Vinson D, Molet-Benhamou L, Degboé Y, et al. Impact of tapering targeted therapies (bDMARDs or JAKis) on the risk of serious infections and adverse

events of special interest in patients with rheumatoid arthritis or spondyloarthritis: A systematic analysis of the literature and meta-analysis. Arthritis Res Ther. 2020;22:97.

165. Van der Leeuw MS, Messelink MA, Tekstra J, et al. Using real-world data to dynamically predict flares during tapering of biological DMARDs in rheumatoid arthritis: development, validation, and potential impact of prediction-aided decisions. Arthritis Res Ther. 2022;24:74.

166. Bechman K, Sin FE, Ibrahim F, et al. Mental health, fatigue and function are associated with increased risk of disease flare following TNF inhibitor tapering in patients with rheumatoid arthritis: An exploratory analysis of data from the Optimizing TNF Tapering in RA (OPTTIRA) trial. RMD Open. 2018;4:e000676.

APPENDICES

Der blev ikke fundet nogen elementer til indholdsfortegnelsen.

Appendix A. Paper I

Appendix B. Paper II

Appendix C. Paper III

Appendix D. Paper IV