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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)

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ABSTRACT

Introduction The The BIOlogical Dose OPTimisation (BIODOPT) trial is a pragmatic, multicentre, randomised controlled, open-label, parallel-group, equivalence study designed to evaluate tapering of biological disease-modifying antirheumatic drugs (bDMARDs) in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) in sustained clinical remission or low disease activity (LDA). Traditionally, these patients maintain standard dosage of bDMARD lifelong; however, recent studies indicate that a significant proportion of patients in sustained remission or LDA can taper their bDMARD and maintain stable disease activity. Thus, this trial aims to evaluate whether a disease activity-guided tapering strategy for bDMARDs will enable a significant dosage reduction while maintaining disease activity compared with usual care. From the individual patient's standpoint as well as from a societal perspective, it would be advantageous if bDMARDs could be reduced or even discontinued while maintaining disease activity.

Methods and analysis A total of 180 patients with RA, PsA or axSpA treated with bDMARDs and in clinical remission/LDA during the past 12 months will be enrolled from four centres in Denmark. Patients will be randomised in a ratio of 2:1 to either disease activity-guided tapering of bDMARDs (intervention group) or continuation of bDMARDs as usual care (control group). The primary objective is the difference between the two groups in the proportion of patients who have reduced their inclusion dosage of bDMARDs to 50% or less while maintaining stable disease activity at 18 months follow-up.

Ethics and dissemination The study is approved by the ethics committee of Northern Jutland, Denmark (N-20170073) and by the Danish Medicine Agency. Patient research partner KHH contributed to refinement of the protocol and approved the final manuscript. Results will be disseminated through publication in international peer-reviewed journals.

Trial registration number 2017-001970-41; Pre-results.

Strengths and limitations of this study

- Randomised controlled, equivalence trial evaluating tapering of biological disease-modifying anti rheumatic drugs (bDMARDs) in relation to disease activity among patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis.
- Involvement of a patient research partner.
- Dosage reduction algorithm is feasible to implement as a pragmatic ('real-world') setting.
- Inability to design and perform the study as a double-blinded trial.
- Heterogeneity across the study population regarding diagnosis and bDMARDs may limit analyses.

INTRODUCTION

Over the last decades, the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) such as tumour necrosis factor (TNF)-α blockers, interleukin-6 receptor blockers and costimulation blockers together with the treat to target paradigm have significantly improved treatment options for patients with inflammatory arthritis such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA).[1–9] To date, the treatment strategy has focused on initial efficacy aiming for low disease activity (LDA) or even remission.

Thus, standard dosage is often continued lifelong to maintain disease control despite limited evidence that it is necessary. Dosage reduction or discontinuation of bDMARDs is an important topic in light of the increasing number of patients who reach remission or LDA and the risk of unnecessary adverse events due to overtreatment, for example, infections. To our knowledge, no treatment guidelines states precisely how tapering of bDMARDs in patients with RA, PsA or axSpA in sustained remission or LDA should be done, that is, at which frequency the dose should be reduced or the dosing interval prolonged.[10–15]

Previous literature show that discontinuation of a bDMARD without prior dosage reduction leads to flare in up to 40%–75% of patients with RA,[16 17] 76%–100% of patients with axSpA[18] and 55%–100% of patients with PsA.[19–21] Thus, abrupt discontinuation of bDMARDs results in flare in a significant proportion of patients. Another approach is to use a tapering algorithm to gradually reduce dosage or increase the dosage interval of bDMARDs to identify patients who can taper or even discontinue their bDMARD. Recent studies indicate that a significant proportion of patients can taper their bDMARDs and still maintain remission or LDA.[16–18 22–29] van Herwaarden *et al* showed that a disease activity-guided tapering strategy of adalimumab or etanercept for patients with RA was non-inferior to usual care when considering major flaring.[30] In the tapering group 18 months from baseline, adalimumab or etanercept were successfully discontinued in 20% of the patients, and the dosage interval was successfully increased in 43%; yet, no dosage reduction was possible for 37%. In the extension phase, safety and efficacy of the disease activity-guided tapering strategy of adalimumab or etanercept was maintained at 3 years from baseline.[31] Fautrel *et al* did not disprove the null hypothesis of non-inferiority in the STRASS study due to insufficient recruitment; however, in the tapering group 18 months from baseline adalimumab or etanercept were successfully stopped in 39.1% and successfully tapered in 35.9% while standard dose had to be maintained in 20.3%.[32] A non-inferiority trial including ankylosing spondylitis (AS) in remission on adalimumab, etanercept, infliximab or golimumab, which was stopped prematurely due to funding problems, found that prolonging the dosing interval of anti-TNF by 25% was non-inferior to full-dosage anti-TNF as LDA was maintained in 81.3% of patients in the tapered group and 83.8% of patient in the full-dose group.[22] In addition, Cantini *et al* showed in a randomised controlled trial (RCT) that 90.4% of patients with AS on full-dose etanercept and 86.3% of patients with AS on half-dose etanercept was still in remission after a mean follow-up of 21–22 months.[33] Furthermore, prospective observational studies in AS and axSpA have proven that a large proportion of patient maintain remission/LDA after tapering of bDMARDs.[34 35] To our knowledge, there are currently neither equivalence nor non-inferiority trials exploring tapering of bDMARDs in patients with PsA using a disease activity-guided algorithm. However, a prospective observation study has shown that 72% of patients treated with 25 mg etanercept maintained remission 1 year after a progressive dosage reduction with 21% receiving weekly dosage and 51% receiving a dosage every-other-week.[27] Additionally, in a case–control study including patients with PsA and RA in remission on adalimumab, the proportion of patients maintaining remission was statistically significant higher among patients with PsA (88.6%) than RA (17.6%) after 50% dosage reduction.[28]

The BIOlogical Dose OPTimisation (BIODOPT) trial is a pragmatic, multicentre, randomised controlled, open-label, parallel-group, equivalence study as a small dosage reduction in bDMARDs is allowed in the control group as usual practice in Denmark; hence, the trial will assess the implementation of a disease activity-guided tapering algorithm for bDMARD compared with usual care. Thus, the aim of this study is to evaluate whether a disease activity-guided tapering strategy for bDMARDs will enable a significant dosage reduction while maintaining disease activity assessed 18 months from baseline compared with usual care. The secondary aims are to identify possible prognostic factors for flare as well as predicting patients who are likely successful dosage reduction candidates. Additionally, we assess if decreased use of bDMARDs in the intervention group will result in a lower rate of adverse events; for example, infections.

METHODS AND ANALYSIS

Patient and public involvement

Collaboration between patients and health professionals during initiation and conduct of research trials provides both parties with shared knowledge.[36] Two patient research partners were included in the initial development of this protocol after the research question was developed. One of the patient partners has provided additional advice incl. assessment of the burden of the intervention; thereby, contributing to and approving the final protocol manuscript and final patient trial information. No patient partners is involved in recruitment or conduct of the trial. Trial results will be disseminated to the participants from research personnel.

Study design

The trial is a pragmatic, multicentre, randomised controlled, open-label, parallel-group, equivalence trial of 18 months duration conducted at four locations in Denmark. After the intervention period, a follow-up examination will be performed at 24 and 60 months from baseline as seen in figure 1A and figure 1B.

Participants and settings

Patients diagnosed with RA, PsA (peripheral) or axSpA (incl. axial PsA) in sustained remission or LDA on bDMARDs are considered for inclusion and will receive written and oral information about the trial by the investigator. Patients will be included in the trial if they fulfil the eligibility criteria and have signed the informed consent

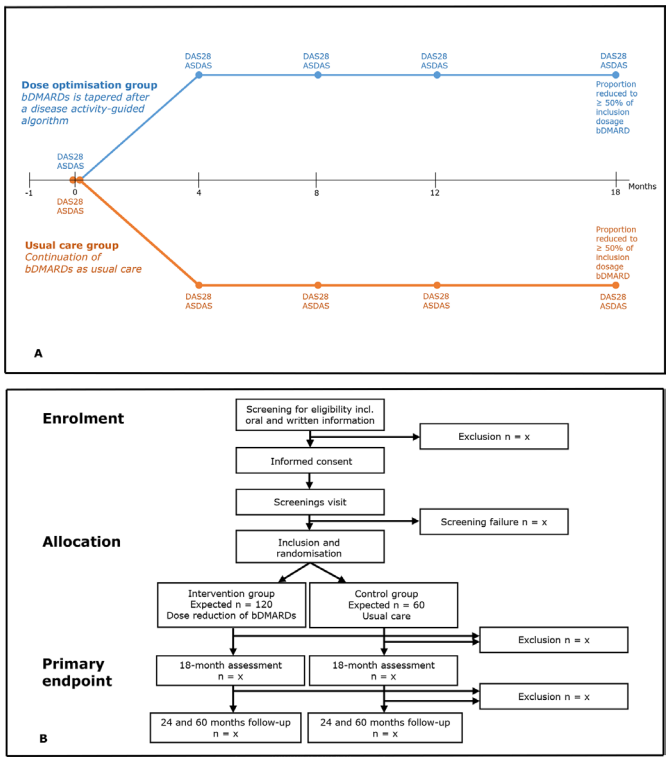

Figure 1 (A,B) An overview of the BIODOPT trial incl. intervention groups and subsequent follow-up visits (after primary endpoint). ASDAS, Ankylosing Spondylitis Disease Activity Score; bDMARDs, biological disease-modifying antirheumatic drugs.

form. Patients are recruited at routine visits at four rheumatology outpatient clinics in Denmark: Aalborg University Hospital, Aarhus University Hospital, Odense University Hospital and The Hospital of South West Jutland, Esbjerg.

Inclusion criteria

- ≥ 18 years of age.
- RA diagnosed by the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria,[37] and/or 1987 ACR RA criteria,[38] axSpA diagnosed by the 1984 modified New York criteria for ankylosing spondylitis,[39] and/or 2009 Assessment of SpondyloArthritis (ASAS) classification of axSpA,[40] and/or PsA according to CLASsification criteria for Psoriatic ARthritis (CASPAR)[41] and/or Moll and Wright criteria.[42]
- Treatment with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or tocilizumab incl. biosimilars in stable dosage during the last 12 months.
- Sustained remission or LDA (as defined by the disease activity criteria for enrolment below) during the last 12 months measured by ≥2 registrations in the Danish Rheumatology Database (DANBIO).
- For female participants with childbearing potential: a negative pregnancy test at baseline and practising safe birth control.

Exclusion criteria

- Current oral prednisolone treatment.
- Intra-articular or parenteral administration of corticosteroids or a short course of oral prednisolone within the last year.
- Dosage reduction of bDMARDs is not suitably judged by medical expert.
- Female participants who are pregnant or breast-feeding or considering becoming pregnant.
- Participants with a history of psychiatric or psychological conditions that, in the opinion of the investigator, will affect the ability to participate in the trial.
- Addictive or previous addictive behaviour.

Disease activity criteria for enrolment

The disease activity criteria for inclusion is: (1) RA: Disease Activity Score28crp (DAS28crp)<3.2[43] and no swollen joints assessed by 46 joint count, (2) PsA: Disease Activity in PSoriatic Arthritis (DAPSA)≤14[44] and no swollen joints assessed by 66/68 joint count and (3) axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS)<2.1[45] and if additional peripheral involvement no swollen joints assessed by 66/68 joint count.

Flare criteria

We define that an arthritis flare in this study requires exclusion of other reasons for flare, for example, infection, lack of adherence or short pause in bDMARD therapy, for example, due to surgery. The flare criteria are: (1) RA and PsA: ΔDAS28crp>1.2 or ΔDAS28crp>0.6 and current DAS28crp≥3.2 and (2) axSpA: inflammatory back pain (assessed by the physician) and ΔASDAS ≥0.9 and/or ≥1 swollen joint assessed by 66/68 joint count.

Patients who flare due to dosage reduction will go one step back in the algorithm, that is, to the dosage of bDMARD before the arthritis flared. Intra-articular steroid and/or a short course of Non-Steroidal Anti-Inflammatory Drugs (NSAID) (max 14 days) are allowed to treat a flare. Patients with sustained flare and no effect of dosage increase are treated in accordance with the national guidelines, for example, switch to another bDMARD.

If a patient has symptoms of psoriasis, uveitis or inflammatory bowel disease (IBD) flare during tapering, the relevant department is contacted for dialogue and expert opinion in particular indication for bDMARD dosage escalation.

Interventions

Participants are randomised in ratio 2:1 to either the intervention group or the control group. Disease activity is monitored at the rheumatology outpatient clinics every 4 months during the first year; thereafter, the primary endpoint assessment is scheduled at 18 months from baseline. A long-term follow-up visit will be performed at 24 and 60 months from baseline. During the BIODOPT trial, disease activity incl. flare is assessed by DAS28crp[46]

for patients with RA and PsA and by ASDAS[47] for patients with axSpA.

At baseline, patients in both trial groups are educated about symptoms of flare by research personnel, for example, increasing peripheral joint pain and/or joint swelling and/or increasing inflammatory back pain. If such symptoms occur, the patients are advised to contact the rheumatology outpatient clinic for a consult within 7 days.

Intervention (BIODOPT) group

In the intervention group, dosage reduction of bDMARDs is done stepwise throughout the first year according to a disease activity-guided algorithm until flare or discontinuation. Thus, bDMARD can be withdrawn after 12 months if disease activity is maintained.

If the patient has symptoms of flare due to tapering but the arthritis is in remission assessed by the physician, the patient is advised to continue tapering according to the BIODOPT algorithm but may remain at the current dosage (or even go back one step in the algorithm).

Patients on reduced dosage of bDMARDs at baseline (relative to standard dosage) are reduced to the nearest level in the algorithm at the first dosage reduction.

Comparator (control) group

In the control group, bDMARDs are continued as usual care. Thus, standard dosage of bDMARDs is continued throughout the study period for most patients, but according to usual care practice in Denmark, the patient and physician can decide to taper bDMARDs by a small increase in the dosage interval.

The BIODOPT algorithm

In the intervention group, dosage of bDMARDs (incl. biosimilars) is reduced gradually over 12 months by prolonging the dosage intervals. The algorithm is used to minimise the risk of flare due to rapid dosage reduction. As long as the patients are in remission, they continue to adhere to the dosage reduction algorithm. Dosage of bDMARDs (excluding infliximab) is reduced with approximately 25% every 4 months, see figure 2A. As infliximab is administered at longer dosage intervals, the algorithm is different; hence, the dosage interval is prolonged with 2 weeks at each infusion, see figure 2B.

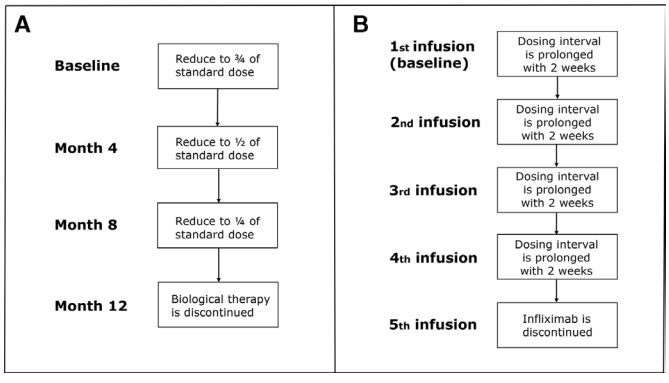

Figure 2 The dosage reduction algorithm for (A) all bDMARD excluding infliximab and (B) infliximab. bDMARD, biological disease-modifying antirheumatic drugs.

Drug accountability

BATCH numbers of the study drug will be registered by research personnel when the intravenous bDMARD is administered or when the subcutaneous bDMARD is handed out to the patient in the outpatient clinic. At each trial visit, drug accountability incl. compliance to the intervention group is recorded. The participant is given a patient journal at each trial visit to keep track of any study drug change, for example, pause due to infection.

Baseline concomitant synthetic DMARD and/or NSAID dose are maintained throughout the study period; however, dosage can be reduced or discontinued if the patient experiences substantial side effects.

Demographic data and medical history

At baseline, the patients' medical history incl. demographic data are obtained through patient interviews and the patients' medical records. Table 1 illustrates a schematic overview of the scheduled assessments incl. the demographic and medical history with subsequent outcomes collected during the BIODOPT trial.

Patient reported outcome measures

As is usual practice in Denmark, patient reported outcome measures are collected electronically through the touchscreen in the outpatient clinic as shown in table 1. Additionally, the Short Form Health Survey 36 (SF-36)[48] is assessed in paper form at each trial visit in order to assess as many aspects as possible of the patient's experience during tapering of bDMARDs.

Clinical and laboratory assessment

The clinical and laboratory assessments performed during the BIODOPT trial are shown in table 1.

Imaging

Radiological examinations including MRI are conducted in accordance with national guidelines for treatment change and not as part of this trial.

Randomisation

All patients will be randomly allocated in permuted blocks of three to six by a computer-generated randomisation sequence with an allocation ratio of 2:1, stratified by trial site (Aalborg, Aarhus, Odense or Esbjerg), diagnosis (ie, RA, axSpA or PsA) and repeated bDMARD failure (currently on bDMARD number 1–2 or higher). SAS PROC PLAN was used to generate the 24 mutually independent randomisation schedules (4 centres×3 diagnoses×2 bDMARD 'stages'); SAS statistical software V.9.4. The randomisation sequence was performed by the senior biostatistician with no clinical involvement in the trial (RC).

Table 1 Overview of assessments in the BIODOPT trial

	Baseline				Endpoint	Follow-up 1	Follow-up 2
Month	0	4	8	12	18	24	60
Demographic data	X						
Medical history	X						
Patient reported outcome measures							
Visual Analogue Scale (VAS) pain (0–100)[64 65]*	X	X	X	X	X	X	X
VAS global (0–100)*	X	X	X	X	X	X	X
VAS fatigue (0–100)*	X	X	X	X	X	X	X
Health Assessment Questionnaire Disability Index (0–3)[66]*	X	X	X	X	X	X	X
Short Form Health Survey 36	X	X	X	X	X	X	X
Bath Ankylosing Spondylitis Disease Activity Index (0–100)[67]*†	X	X	X	X	X	X	X
Bath Ankylosing Spondylitis Functional Index (0–100)[68]*†	X	X	X	X	X	X	X
Clinical assessments							
Height (cm) and weight (kg)	X						
Blood pressure (mm Hg) and pulse (beats/minute)	X						
Swollen and tender joint count (number)‡	X	X	X	X	X	X	X
Bath Ankylosing Spondylitis Metrology Index (0–100)[69]†	X	X	X	X	X	X	X
Spondyloarthritis Research Consortium Canada Enthesitis score[70]§	X	X	X	X	X	X	X
Dactylitis (0–20)§	X	X	X	X	X	X	X
Psoriasis Area Severity Index score[71]§	X	X	X	X	X	X	X
Modified Nail Psoriasis Severity Index score[72]§	X	X	X	X	X	X	X
VAS physician (0–100)[64]	X	X	X	X	X	X	X
Adverse events incl. infections	X	X	X	X	X	X	X
Composite scores							
Disease Activity Score28crp¶	X	X	X	X	X	X	X
Ankylosing Spondylitis Disease Activity Score‡	X	X	X	X	X	X	X
Laboratory assessments							
Routine blood tests**	X	X	X	X	X	X	X
Baseline blood tests††	X						
ACPA, IgM-RF, ANA	X						
HLA-B27‡	X						
Biomarker collection for biobank	X	X	X	X	X	X	X
Blood human chorion gonadotropin (B-hCG)‡‡	X						
Imaging							
X-ray hands and feet¶	X				X		
X-ray SI joints‡	X				X		

*Registered electronically through the touch screen in the outpatient clinic.
†Assessed for patients with axSpA.
‡46 joint count for patients with RA and 66/68 joint count for patients with PsA or axSpA.
§Assessed for patients with PsA and axSpA.
¶Assessed for patients with RA and PsA.
**C-reactive protein, haemoglobin, differentiated white cell count, platelets, creatinine, alanine transaminase and alkaline phosphatase.
††Uric acid, thyroid-stimulating hormone, vitamin D status.
‡‡Performed in women of childbearing potential at baseline.
ACPA, anti-cyclic citrullinated peptide; ANA, antinuclear antibody; axSpA, axial spondyloarthritis; HLA, human leukocyte antigen; IgM-RF, immunoglobulin M-rheumatoid factor; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SI, sacroiliac joint.

Allocation concealment and implementation

The allocation sequences are concealed in a password-protected computer file only accessible by the senior biostatistician (RC) and an independent data manager. The independent data manager entered the randomisation sequence in the electronic case report form (e-CRF) in REDCap. When enrolled, the participants will be randomised and given their randomisation group when the physician 'clicks' on the 'randomisation button' in the e-CRF in REDCap. The assigned intervention will then be visible on the screen. Thus, the patients are given randomisation numbers independent of the trial site with concealed group allocation.

The interventions in this trial are not blinded.

Primary outcome

The primary objective is to evaluate whether a disease activity-guided tapering strategy for bDMARDs will enable a significant dosage reduction while maintaining disease activity assessed 18 months from baseline compared with usual care. Thus, there are two primary efficacy endpoints:

1A Superiority: The proportion of patients who at 18 months are reduced to 50% or less of their inclusion dose of bDMARD.

1B Equivalence: Disease activity assessed 18 months from baseline.

The primary objective is met if a statistically significant reduction in biologics is demonstrated while maintaining an equivalent disease state.

Secondary outcomes

Secondary outcomes are listed in table 1 and include identifying possible prognostic factors for flare as well as predictors for candidates likely for successful dosage reduction of bDMARDs. Additionally, adverse event rates are examined in both groups to evaluate if decreased use of bDMARDs in the intervention group will result in a lower rate of adverse events, for example, infections.

Tertiary (exploratory secondary) outcomes

Tertiary outcomes are to explore, if blood levels of cytokines, drug-level, antidrug–antibodies or changes in these variables from baseline are a predictor for flare or successful dosage reduction.

Statistical methods

Sample size and power considerations

The sample size calculation is done in accordance with the DELTA^2 guideline for reporting sample size calculations in RCTs.[49]

1A: We assume that 30% of the patients allocated to the intervention group and 5% of patients allocated to the control group will meet primary endpoint 1A. This assumption is inspired from the DRESS-RA trial, which it is one of the very few randomised, non-inferiority/equivalence trials exploring a disease activity-guided tapering algorithm among patients with inflammatory arthritis.[30] No randomised, non-inferiority/equivalence study exploring a disease activity-guided tapering algorithm was to our knowledge published in PsA or axSpA when the sample size calculation was performed; however, based on the available literature, it seems reasonable to assume that the percentage of patients with PsA or axSpA meeting primary endpoint 1A will be the same as for RA.[22 27 28 33] Thus, the sample size calculation was not done for each disease separately.

For a comparison of two independent binomial proportions using Pearson's χ^2 statistic with a χ^2 approximation with a two-sided significance level of 0.05, a total sample size of 180 assuming an allocation ratio of 2:1 has a very high statistical power of 0.992 (99%) if the proportion of patients significantly reducing their bDMARDs (≥50% reduction) are 30% and 5%, respectively.

1B: For the between-group comparison, members of the BIODOPT trial group (SK, AS, EMH and LU) decided a predefined margin of equivalence at ±0.5 DAS28crp points for patients with RA or PsA and ±0.5 ASDAS points for patients with axSpA. This margin was determined based on 'less than half of the effect' that would be considered a clinically relevant reduction in DAS28crp level (ΔDAS28crp>1.2) or ASDAS level (ΔASDAS >1.1) corresponding to a clinically unimportant change in arthritis disease activity. In a two one-sided test analysis for additive equivalence of two-sample normal means with bounds±0.5 for the mean difference and a significance level of 0.05, assuming a mean difference of 0 and a common SD of 1.0, a total sample size of 180 participants assuming an allocation ratio of 2:1 yields a sufficient statistical power of 0.868 (87%). The sample size was determined from the power of the coprimary endpoint with the least statistical power, that is, primary endpoint 1B which is why the power for superiority of 0.992 appears extremely high. Thus, inclusion of 180 patients (randomised 2:1) in total during an inclusion period of 1 year is planned.

Drop-out considerations is based on primary endpoint 1B, as this is the endpoint with the lowest power (0.868). In a two one-sided test analysis for additive equivalence of two-sample normal means with bounds −0.5 and 0.5 for the mean difference and a significance level of 0.05, assuming a mean difference of 0 and a common SD of 1, a total sample size of 156 assuming an allocation ratio of 2:1 is required to obtain a power of at least 0.8 (power=0.802). Thus, 24 drop-outs (180–156) are allowed corresponding to 13%.

Statistical analysis

All descriptive statistics and tests will be reported in accordance to the recommendations of the Enhancing the QUAlity and Transparency Of Health Research network[50] including the Consolidated Standards of Reporting Trials statements.[51 52] Thus, all data analyses will be carried out according to a pre-established statistical analysis plan. The analyses for the primary and secondary endpoints will be conducted according to the ITT principle; that is, based on the full analysis set (all randomised individuals independent of protocol violations) with outcome data available (as observed).[53] For the equivalence analyses

(ie, according to disease activity), imputations will not be used to replace missing data in the primary analyses, but will be included in a sensitivity analysis to assess the effect of missing data. Thus, ITT analyses with replacement of missing data as well as analysis on 'per protocol' individuals will only be performed to explore the robustness of our findings.

To evaluate the longitudinal effects of the intervention, all continuous outcome variables (eg, disease activity (1B)) will be analysed using a multilevel repeated-measures linear mixed effects model, with participant as random effect factor based on a restricted maximum likelihood model. The model will include group (ie, intervention vs usual care), diagnosis, bDMARD failure history, centre status and time point (4, 8 and 12 months from baseline) as fixed effects, with the baseline value of the relevant variable (eg, disease activity (1B)) as a covariate. A two-sided 95% CI for the difference in disease activity at 18 months follow-up between groups will be derived from the repeated-measures mixed linear model and equivalence will be declared if the 95% CI of disease activity level is completely within the prespecified equivalence range (−0.5 units to +0.5 units). Dichotomous end points (eg, number of participants who achieve a significant reduction in bDMARDs (≥50%) while assessed after 18 months) will be analysed with the use of simple logistic regression with the same fixed effects and covariates as the respective analysis of covariance; unlike the continuous outcome proportions responding will only be analysed following 18 months.

For the superiority tests (eg, composite primary endpoint (1A)), we set the statistical significance at the conventional level of 0.05 ($p<0.05$). Results will be expressed as estimates of the differences between groups, with 95% CIs to represent precision of the estimates. Multiplicity considerations clearly play a central role in the assessment of efficacy evidence in the presence of competing clinical objectives (eg, composite primary endpoints).[54] In the BIODOPT trial, we apply a hierarchical primary endpoint in order to adjust for the fact that the more tests you do, the more likely it is that a comparison appear as falsely significant. In the BIODOPT trial, the primary superiority objective is to reduce the use of bDMARDs in patients with inflammatory arthritis (by at least 50%) compared with the control group, while still maintaining a similar disease control (equivalence). Because this trial will have two potential 'efficacy claims', a hierarchical test approach will be used to preserve the overall type I error rate at a two-sided alpha level of 0.05. The overall error rate will be split between the endpoints: in the BIODOPT trial, the primary statistical tests have two steps. In step #1, we will assess the superiority claim of the BIODOPT intervention being better than control leading to reduced use of bDMARDs ($p<0.05$), while step #2 constitutes an equivalence claim, if and only if, step 1 is statistically significant and the 95% CI around the between-group difference in disease is precise enough: 95% CI: −0.5 to 0.5 disease activity units.

In addition, exploratory subanalysis will be performed to evaluate the effect of, for example, bDMARD drug.

Data collection

Research personnel at each trial site will schedule participant appointments and together with the coordinating investigator monitor participant retention to minimise the risk of missing data. If a participant misses a scheduled trial visit, he/she will be contacted by research personnel to schedule a new visit. Reasons for non-adherence and non-retention will be recorded.

Data are collected in an e-CRF in REDCap only accessible to research personnel by username and password. REDCap use data logging to create an audit trail thereby registering who is looking at, changing or entering data. Data quality will be promoted through the REDCap features real-time data entry validation (eg, for dates and range checks) and required data entry at each clinical visit. Thus, all trial-related information will be stored securely in REDCap with the exception of paper forms which will be stored securely at the trial sites. The BIODOPT trial complies with the Danish laws regarding patient confidentiality and is reported to the Danish Data Protection Agency. Data will be destroyed 15 years after the end of the trial.

The BIODOPT trial group will have access to the final data set. In addition, investigators will have access to the final data set from their own site.

Adverse events

All adverse events reported from baseline to the end of this trial will be registered and followed by the investigators to a satisfactory conclusion. An arthritis flare is not considered an AE. The investigators must report any serious adverse event or serious adverse reaction to the sponsor–investigator and coordinating investigator within 24 hours. A suspected unexpected serious adverse reaction will be reported to the medical products agency, the local ethics committee, the Danish Medicines Agency and the trial investigators within 7 days if judged to be life threatening otherwise within 15 days.

The section 'adverse reactions' in the product information of the bDMARDs are used as referral documents for adverse events assessment.

Data registration and monitoring

The BIODOPT trial is conducted in compliance with the protocol, Good Clinical Practice (GCP) and all other applicable regulatory requirements. Before start of participant enrolment (17 May 2018), the trial was confirmed as registered at EudraCT (21 December 2017). The trial is monitored in accordance with the GCP monitoring plan by the local Danish GCP units at Aarhus, Aalborg and Odense University Hospitals to ensure that the trial is carried out in accordance with the protocol, IH-GCP and Danish laws.

ETHICS AND DISSEMINATION

Informed consent for the BIODOPT trial and for storage of blood in a biobank will be obtained from all patients

before study enrolment by the investigators. Patients can discontinue the trial prematurely without any consequences for their future arthritis treatment; hence, they will receive standard arthritis care according to the national Danish guidelines.

Prior studies on this subject have found no considerable adverse events when tapering bDMARDs in patients with RA, PsA or axSpA in sustained clinical remission or LDA as a flare is treated successfully when escalating to standard dosage bDMARDs in most patients[28 29 33 34 55–58]; however, in a smaller proportion of patients switching to a different bDMARD can be necessary to gain remission/LDA.[33 55 58 59] When considering the well-known dose-dependent risk of serious infection in arthritis patients treated with bDMARDs,[60] it is expected that the intervention group will have a smaller risk of adverse events incl. serious infections compared with the control group. In light of the above and the well-documented safety profile of the study drugs, a data monitoring committee will not be used during the conduct of this trial.

This trial is expected to contribute with new knowledge about dosage reduction of bDMARDs in patients with RA, PsA and axSpA in sustained remission/LDA; thereby, providing possible benefits for arthritis patients and the society. In light of the above, we consider it ethically justifiable to conduct the trial.

Important protocol amendments require approval by the local Ethics Committee and the Danish Medicines Agency prior to implementation. The coordinating investigator will notify investigators at the trial sites.

All results of this trial both negative, inconclusive and positive will be reported; preferably, in English-language peer-reviewed medical journals as well as presented at international congresses. All persons designated as authors will qualify for authorship based on the ICMJE recommendations.

DISCUSSION

To our knowledge, the BIODOPT trial is the first pragmatic, randomised controlled, equivalence study exploring a disease activity-guided tapering algorithm of bDMARDs in patients with RA, PsA or axSpA in sustained remission or LDA. The trial design with a coprimary endpoint of which 1A aims for superiority and 1B aims for equivalence was chosen, as we expect dosage reduction of bDMARDs by the BIODOPT algorithm to be superior in dosage reduction of bDMARDs but equivalent in maintaining disease activity compared with usual care. The randomised controlled design with a comparator group receiving bDMARDs as usual care will provide statistical evidence evaluating dosage reduction of bDMARDs; thereby, contributing with important, new information.

The randomisation ratio was set to 2:1 (intervention group:control group) in order to obtain more data on the intervention group for subanalyses; however, it should be noted that the study is not powered to find a statistically significant difference between the disease groups nor the different bDMARDs but exploratory analyses will be made.

The BIODOPT trial is to our knowledge the first randomised, equivalence trial exploring a disease activity-guided tapering algorithm of seven different bDMARDs including biosimilars among patients with inflammatory arthritis. However, a limitation is that the trial personnel and the patients are not blinded to the intervention groups; thus, this could potentially lead to bias, for example, expectation and/or attribution bias which would affect interpretation of the trial results. After the primary endpoint assessment at 18 months, the patients will be followed up at 24 and 60 months from baseline; hence, data from these visits will give an important insight into the long-term effects of dosage reduction of bDMARDs.

As usual care practise in Denmark, the patient is an equal partner in his/her disease management; thus, the patient can remain at the current dosage of bDMARDs or even go back one step in the algorithm after agreement between the patient and physician.

Regarding the disease activity criteria for enrolment, DAS28crp was chosen for RA as a review of patients with RA from the Department of Rheumatology at Aalborg University Hospital showed that only 1 patient out of 31 treated with bDMARDs who fulfilled DAS28crp remission but not CDAI remission had swollen joints, the remaining patients were not in CDAI remission because of a high patient VAS global disease activity. For patients with axSpA, ASDAS was selected over BASDAI as it is the recommended index by ASAS and EULAR.[14] At present, there is to our knowledge no consensus regarding the preferred efficacy parameter for patients with PsA; however, DAPSA was chosen in this trial, as it is a stringent index that contains 66/68 joint count for swollen and tender joints and is one of the suggested efficacy scores by EULAR.[10] Steroid treatment during the past year is listed as an exclusion criteria to ensure that the participants are in steroid-free remission/LDA at baseline.

In existing studies, it has been discussed if disease activity at baseline could be an effect modificator for successful tapering but the results were conflicting.[61] However, in a recent systematic review by Tweehuysen *et al* it was concluded, that disease activity at baseline, that is, remission or LDA, was not an effect modificator for successful tapering of bDMARDs.[61] Consequently, the inclusion criteria for disease activity for this trial was expanded after start of recruitment after approval of the relevant authorities; thus, patients with RA, PsA or axSpA in remission or LDA with no swollen joints will be enrolled. Inclusion of patients in both remission and LDA will improve the generalisability of the trial results.

In this trial, the ASAS definition of ASDAS worsening is used as a flare criteria for axSpA[62] and the OMERACT recommended DAS28 flare criteria for patients with RA.[63] As no arthritis flare criteria exist for patients with PsA, the DAS28 flare criteria are also used for this patient group. However, we acknowledge that it would be desirably to

monitor patients with PsA using a PsA-validated flare criteria, for example, a DAPSA-based flare criteria as DAPSA is used as remission criteria for enrolment in this trial. Nevertheless, DAPSA will be calculated for patients with PsA for each trial visit for further subanalysis. In addition, PsA and axSpA essential outcomes as skin involvement, nail involvement, enthesitis and dactylitis will be monitored; hence, subanalysis will be performed and information about reason for dosage escalation of bDMARDs due to extra-articular manifestations will be collected , for example, psoriasis skin flare.

Tapering of bDMARDs is an important topic as an increasing number of arthritis patients reach sustained remission or LDA and continuation of standard dosage potentially can lead to overtreatment and unnecessary side effects such as infections. Dosage reduction by increasing the interval will result in less visits to the outpatient clinic for IV infusions or longer interval between subcutaneous injections, which is expected to decrease the individual patient's disease burden. In addition, bDMARDs are costly; thus, benefits for society (incl. costs) could be anticipated. In addition, we expect the results from the prognostic factor research to contribute with new, important information; hence, guiding and facilitating a shared decision-making regarding dosage reduction of bDMARDs for everyday clinical practice. Thus, the BIODOPT trial will contribute with new information, which can be used for guidance in the attempt to qualify the discussion on how to taper bDMARDs in patients with inflammatory arthritis in sustained remission or LDA. Therefore, we believe that the BIODOPT trial will lead to a significant change in the clinical management of these patients.

Trial status

Recruitment started with first patient first visit on 17 May 2018 and is expected to last until 1 September 2019 or until the target population is reached. The co-ordination investigator will monitor enrolment rate during the inclusion period and send out a monthly newsletter with recruitment status to motivate investigators and research nurses.

The BIODOPT trial is currently running with first patient last visit scheduled for November 2019 and last patient last visit expected to be in February 2021.

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Contributors LU, SK and AS conceived the trial hypothesis and LU, SK, AS, EMH and RC have designed the trial. SK is the trial sponsor-investigator and LU is the coordinating investigator. LU, SK, AS, EMH, RC and LD are responsible for implementation of the trial, analysis of the results and publication in scientific journals. LU, SK, AS, EMH and RC all contributed to refinement of the trial protocol and approved the final manuscript. LU wrote this protocol paper and SK, AS, LD, EMH, RC and MESA contributed with refinement and approved the final draft.

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Competing interests LU has received speaker honoraria from Abbvie, Eli Lilly and Novartis (not related to the submitted work). SK has received speaker honoraria from Novartis and Eli Lilly (not related to the submitted work). AS has received speaker honoraria from MSD and Eli Lilly (not related to the submitted work). LD has received speaker honoraria from UCB, MSD, Eli Lilly and Janssen Pharmaceutica (not related to the submitted work).

Patient consent for publication Not required.

Ethics approval This trial is approved by the ethics committee of Northern Jutland, Denmark (N-20170073) and by the Danish Medicine Agency (2017091722) and the Danish Data Protection Agency (2017–194). The BIODOPT trial is conducted in accordance with the Helsinki Declaration.

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