Ther Adv Musculoskel Dis
2021, Vol. 13: 1–11
DOI: 10.1177/1759720X211057975

Axial Involvement in Psoriatic Arthritis cohort (AXIS): the protocol of a joint project of the Assessment of SpondyloArthritis international Society (ASAS) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)

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Abstract

Background: Involvement of the axial skeleton (sacroiliac joints and spine) is a relatively frequent manifestation associated with psoriatic skin disease, mostly along with involvement of peripheral musculoskeletal structures (peripheral arthritis, enthesitis, dactylitis), which are referred to as psoriatic arthritis (PsA). Data suggest that up to 30% of patients with psoriasis have PsA. Depending on the definition used, the prevalence of axial involvement varies from 25% to 70% of patients with PsA. However, there are currently no widely accepted criteria for axial involvement in PsA.

Objective: The overarching aim of the Axial Involvement in Psoriatic Arthritis (AXIS) study is to systematically evaluate clinical and imaging manifestations indicative of axial involvement in patients with PsA and to develop classification criteria and a unified nomenclature for axial involvement in PsA that would allow defining a homogeneous subgroup of patients for research.

Design: Prospective, multicenter, multinational, cross-sectional study.

Methods and analyses: In this multicenter, multinational, cross-sectional study, eligible patients [adult patients diagnosed with PsA and fulfilling Classification Criteria for Psoriatic Arthritis (CASPAR) with musculoskeletal symptom duration of ⩽10 years not treated with biological or targeted synthetic disease-modifying anti-rheumatic drugs] will be recruited prospectively. They will undergo study-related clinical and imaging examinations. Imaging will include radiography and magnetic resonance imaging examinations of sacroiliac joints and spine. Local investigators will evaluate for the presence of axial involvement based on clinical and imaging information which will represent the primary outcome of the study. In addition, imaging will undergo evaluation by central review. Finally, the central clinical committee will determine the presence of axial involvement based on all available information.

Ethics: The study will be performed according to the ethical principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. The study protocol will be approved by the individual Independent Ethics Committee / Institutional Review Board of participating centers. Written informed consent will be obtained from all included patients.

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Registration: ClinicalTrials.gov ID: NCT04434885.

Keywords: axial spondylitis, psoriatic arthritis, spondyloarthritis

Received: 24 June 2021; revised manuscript accepted: 14 October 2021.

Introduction

Psoriasis is an immune-mediated disease mainly affecting the skin and often the nails. Involvement of the axial skeleton [sacroiliac joints (SIJ) and spine] is a relatively frequent manifestation associated with psoriatic skin disease along with involvement of peripheral musculoskeletal structures (peripheral arthritis, enthesitis, dactylitis), which collectively are often referred to as psoriatic arthritis (PsA). Data from cohort studies suggest that up to 30% of patients with psoriasis have PsA.[1,2] Depending on the definition used, the prevalence of axial disease varies from 25% to 70% of patients with PsA.[3–7] Recent data from the CorEvitas registry indicated that the presence of axial involvement (defined as physician-reported presence of spinal involvement at enrolment) is associated with a higher likelihood of moderate/severe psoriasis, with higher disease activity and greater effect on quality of life in patients with PsA.[8]

There is an ongoing discussion as to whether patients with psoriasis and inflammatory axial disease should be diagnosed with 'PsA with axial involvement' [other commonly used terms: psoriatic spondylitis, psoriatic spondyloarthritis (SpA) axial PsA] or with 'axial spondyloarthritis with psoriasis'. Although some features typical for axial involvement in PsA have been described [lower prevalence (as compared with the primary axial SpA without psoriasis) of inflammatory back pain and HLA-B27; isolated involvement of the spine without SIJ], a clear distinction between axial PsA and primary axial SpA is not always possible due to a natural overlap between these conditions. There is also an overlap between the CASPAR (ClASsification criteria for Psoriatic ARthritis) for PsA[9] and ASAS (Assessment of SpondyloArthritis international Society) classification criteria for SpA (both axial and peripheral)[10] resulting from the pathophysiological proximity of the diseases. Currently, there are no widely accepted criteria of axial involvement in PsA. According to the ASAS criteria, patients with PsA can be classified as patients with axial SpA in the presence of chronic back pain with onset prior to the age of 45 years plus presence of sacroiliitis on magnetic resonance imaging (MRI) or radiographs (according to the radiographic criterion of the modified New York criteria) plus one additional SpA feature that can be psoriasis, or alternatively in the presence of HLA-B27 plus 2 additional SpA features.

Data from a recent systematic literature review suggested that PsA patients with axial involvement frequently have characteristics that would not allow classification of patients as axial SpA such as late onset of back pain, involvement of the spine without SIJ, weaker association with HLA-B27, and less frequently an inflammatory character of back pain.[11,12] Furthermore, it is currently unclear whether treatment response in PsA patients with axial involvement can be extrapolated from the data generated in primary axial SpA since only a few studies have been conducted so far in patients with PsA and suspected axial involvement.[13,14] For example, in primary axial SpA, two interleukin (IL)-23 inhibitors (ustekinumab and risankizumab) failed to show clinical efficacy compared with placebo,[15,16] despite good clinical efficacy in psoriasis and PsA with predominant peripheral involvement.[17,18] However, a recent analysis of a subset of patients included in the guselkumab – another IL-23 inhibitor – in PsA who had radiographs or MRI showing sacroiliitis in the opinion of investigator, and high Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, suggests that IL-23 may be effective in treating axial symptoms of PsA.[19] Therefore, there is a need to determine in clinical trials whether these drugs as well as other drugs that have shown efficacy in peripheral manifestations of PsA are also effective in treating the axial PsA.

In general, axial involvement is poorly assessed (or not assessed at all) in trials with PsA. One reason for this is the lack of widely accepted criteria

for axial involvement in PsA that could be used for research purposes. Adding in the variability of axial involvement and the frequent presence of mechanical back disorders, it has been difficult to justify the added measurement burden and expense of longitudinal MRI assessment of the spine and SIJ in the whole study population or even in those with presumed axial involvement, which may vary between study arms. There is an urgent need for classification criteria and a unified and widely accepted nomenclature for axial involvement in PsA that would allow selection of a more homogeneous subgroup of patients among a heterogeneous PsA population.

In 2018, ASAS and GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) agreed to develop a consensus definition and subsequently data-driven classification criteria for axial involvement in PsA to be used for research purposes. Such classification criteria are to be applied to patients with clinically diagnosed PsA to build a more homogeneous group of patients for inclusion in clinical studies. In addition to the conducted literature review,[12] an online survey among ASAS and GRAPPA members was conducted in December 2018–January 2019 to identify the most relevant variables relevant to deciding on the presence of axial involvement in PsA. The four variables with the highest ranking were related to the objective signs of inflammatory changes in the axial skeleton on radiographs or MRI.

Currently, there is no PsA cohort in which a complete set of imaging (plain radiographs and MRI of SIJ and spine) is available in all patients. Therefore, we initiated a prospective cross-sectional study to systematically evaluate clinical and imaging manifestations indicative of axial involvement in patients with PsA.

Methods and analysis

Aim and objectives

The overarching aim of the Axial Involvement in Psoriatic Arthritis (AXIS) study is to systematically evaluate clinical and imaging manifestations indicative of axial involvement in patients with PsA to develop classification criteria and a unified nomenclature for axial involvement in PsA that would allow defining a homogeneous subgroup of patients for research.

The main objectives of the planned study are

1. to determine the frequency of axial involvement in patients with PsA (based on local and central assessments) in the studied patient population;
2. to identify the frequency of active inflammatory and structural changes on imaging (MRI and radiographs) suggestive of axial involvement (SIJ and spine) in PsA; and
3. to identify factors (clinical, laboratory, imaging) associated with the presence of axial involvement in PsA, which will be determined based on the local and central assessments.

Study design

This is a multicenter, multinational, cross-sectional study in patients with a definite diagnosis and classification of PsA. Eligible patients (see Study Population) will be recruited prospectively from approximately 50 study centres in 20 countries and will undergo study-related examinations (see Study Procedures) including imaging (radiography and MRI) of the axial skeleton. These images will be evaluated locally and by the central imaging committee. Collected data will serve as a basis for the determination of the presence of axial involvement by the local investigator and, independently, by the central clinical study committee.

Study population and eligibility

The population of interest will consist of adult patients diagnosed with PsA and fulfilling CASPAR criteria for PsA with musculoskeletal symptom duration of up to 10 years and not receiving biological or targeted synthetic disease-modifying antirheumatic drugs (DMARDs). Participating rheumatologists will be encouraged to include consecutive PsA patients not treated with biologic or a targeted synthetic DMARD because of their potential impact on active inflammatory and structural changes in the axial skeleton, which will be the focus of the current study. Currently, no conclusive data exist for the impact of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, or conventional synthetic DMARDs (such as methotrexate, leflunomide and sulfasalazine) on the inflammatory changes in the axial skeleton; therefore, patients receiving these medications will be eligible. The limited to 10 years symptom

Table 1. Eligibility criteria for the AXIS study.

Inclusion criteria
• Subject ⩾ 18 years of age. • Written informed consent. • Definite diagnosis of PsA. • Fulfilment of CASPAR criteria for PsA. • Duration of PsA symptoms ⩽ 10 years.
Exclusion criteria
• Unable or unwilling to give informed consent or to comply with the protocol. • Current or past treatment with biologic or a targeted synthetic disease-modifying antirheumatic drug (DMARDs). • Contraindications for MRI or plain radiography of sacroiliac joints and spine.

AXIS, Axial Involvement in Psoriatic Arthritis; CASPAR, Classification Criteria for Psoriatic Arthritis; DMARDs, disease-modifying antirheumatic drugs; MRI, magnetic resonance imaging; PsA, psoriatic arthritis.

duration should help to avoid inclusion of PsA patients with long-standing but rather inactive disease (since patients should not be treated with biologic and targeted synthetic DMARDs) that is probably associated with a lower risk of axial involvement. Thus, these inclusion criteria are intended to mitigate the risk of underestimating the frequency of axial involvement in PsA. The full list of inclusion and exclusion criteria of the AXIS study is shown in Table 1.

It is expected that most of the consecutive patients will be presenting with peripheral involvement (arthritis / enthesitis / dactylitis), while patients with pure axial disease will account for less than 5% of the recruited patients. Nevertheless, since the latter patient group represents a potential source for misclassification bias (patients with axial SpA and psoriasis *versus* PsA with axial involvement), we plan the primary analysis to be conducted in the group of patients presenting with peripheral involvement. Patients with axial disease without peripheral involvement will be compared with those with peripheral involvement in a subsequent analysis.

Study procedures

Clinical assessments. The following clinical information will be collected from eligible patients who sign the informed consent and are entered in the electronic database: demographic characteristics; anthropometric measures; date of psoriasis and musculoskeletal symptoms onset; date of psoriasis and PsA diagnoses; positive family history of SpA or related diseases; presence of back pain; presence of inflammatory back pain (global assessment and ASAS criteria); presence of other extra-musculoskeletal manifestations; presence of peripheral arthritis, dactylitis, or enthesitis [with a calculation of the Spondyloarthritis Research Consortium of Canada (SPARCC) score,[20] the Maastricht Enthesitis Score (MASES),[21] and the Leeds Enthesitis Index (LEI)[22]]; spinal mobility assessments including Bath Ankylosing Spondylitis Metrology Index (BASMI);[23,24] current and former treatment of psoriasis and PsA; and physician global assessment of disease activity [0–10 numeric rating scale (NRS)] (see Table 2).

Patient-reported outcome measures. Patient-reported outcome measures include the patient global assessment (NRS),[25] overall pain (NRS), back pain (NRS), Health Assessment Questionnaire (HAQ),[26] spondyloarthritis modification of the HAQ (HAQ-S),[27] Psoriatic Arthritis Impact of Disease Questionnaire (PsAID),[28] the BASDAI,[29] the Bath Ankylosing Spondylitis Functional Index (BASFI),[30] ASAS Health Index,[31] and Work Productivity and Activity Impairment Questionnaire General Health V2.0 (WPAI:GH)[32] (see Table 2).

Laboratory assessment. The laboratory parameters are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and HLA-B*27 status. In addition, deoxyribonucleic acid (DNA) samples (whole blood) will be collected.

Imaging. Imaging of the axial skeleton will include both conventional radiographs and MRI of the SIJ and of the spine. Assuming a high prevalence of axial involvement reported previously, both imaging methods are justified clinically as diagnostic procedures. Conventional radiographs will be performed to capture new bone formation that might not be well depicted on MRI. Specifically, plain radiography of SIJ and spine (cervical and lumbar), and MRI of SIJ and whole spine will be obtained. All obtained images will be collected in the Digital Imaging and Communications in Medicine (DICOM) format to be anonymized and uploaded to the central repository.

Local assessment of imaging and of the presence of axial involvement. The local rheumatologist will indicate the presence or absence of imaging

Table 2. Study procedures.

1. Clinical assessments

Demographic characteristics

- Date of birth (month, year) and corresponding age
- Sex
- Race/ethnicity
- Occupation (manual / non-manual)
- Education level
- Smoking status
- Alcohol consumption
- Anthropometric measures: height and weight

Clinical characteristics and physical examination

- Date of musculoskeletal symptoms onset (axial – back pain, and peripheral – arthritis, enthesitis, dactylitis, symptoms)
- Date of psoriasis diagnosis (if present)
- Date of PsA diagnosis
- Family history (1st and 2nd degree relatives) for axial SpA / ankylosing spondylitis, psoriasis and PsA, inflammatory bowel disease, uveitis.
- Presence of back pain and if present – duration and age at onset
- Presence of inflammatory back pain (global assessment) and of single parameters typical for inflammatory back pain (insidious onset, improvement with exercise, no improvement with rest, morning stiffness of $\geqslant$30 minutes, night pain, alternating buttock pain)
- Good response of back pain to NSAIDs
- Presence of psoriasis, if present – affected BSA and PASI score
- Type of psoriasis (if present)
- Psoriatic nail affection (presence)
- Presence of other extra-musculoskeletal manifestations: inflammatory bowel disease, uveitis
- Presence of peripheral arthritis; 66/68 tender/swollen joint counts
- Presence of dactylitis (including number of digits affected)
- Presence of enthesitis – assessment of enthesitis sites allowing a calculation of the SPARCC score, MASES and LEI to be derived
- Spinal mobility assessment: chest expansion at xiphisternum, cervical rotation, tragus to wall distance, modified Schober test, lateral spinal flexion and intermalleolar distance; the BASMI will be calculated
- Current and former treatment of psoriasis and PsA (local treatment, phototherapy, systemic corticosteroids, NSAIDs, csDMARDs
- Physician global assessment of disease activity (0–10 NRS)

Patient-reported outcome measures

- Patient global assessment (0–10 NRS)
- Overall pain (NRS)
- Back pain (NRS)
- HAQ and HAQ-S
- PsAID
- BASDAI
- BASFI
- ASAS Health Index
- Work Productivity and Activity Impairment Questionnaire General Health

2. Laboratory assessment

- CRP
- ESR
- HLA-B27
- HLA-typing (central lab)

(continued)

Table 2. (Continued)

3. Imaging
Radiography • Plain radiography of sacroiliac joints (conventional AP view of the pelvis) • Plain radiography of spine: cervical spine lateral view, lumbar spine – lateral and anteroposterior views MRI • MRI of sacroiliac joints (semicoronal T1-weighted sequence, semicoronal Short Tau Inversion Recovery Sequence (STIR) or a T2-weighted sequence with fat suppression (T2FS), semicoronal erosion specific sequence (T1FS spin echo / T1 Dixon / 3D gradient echo such as VIBE), semiaxial STIR or T2FS. • MRI of entire spine (sagittal T1-weighted sequence and sagittal STIR or T2FS of the cervical, thoracic and lumbar spine).
4. Local assessment of the presence of axial involvement
5. Central assessment of the presence of axial involvement
• Central imaging committee • Central clinical committee

AP, anteroposterior; ASAS, Ankylosing Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BSA, Body Surface Area; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire, HAQ-S, Spondyloarthritis modification of the Health Assessment Questionnaire; HLA, human leucocyte antigen; LEI, Leeds Enthesitis Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MRI, magnetic resonance imaging; NRS, Numeric Rating Scale; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsAID, Psoriatic Arthritis Impact of Disease; SpA, spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada; STIR, Short Tau Inversion Recovery; VIBE, volumetric interpolated breath-hold examination.

changes indicative of axial involvement on imaging: radiographic sacroiliitis according to the modified New York criteria, presence of radiographic changes indicative of axial involvement in the spine, as well as presence of MRI findings indicative of axial involvement (a global evaluation and separate assessment of the presence of active inflammatory and structural changes) in sacroiliac joints and spine. For each of the global questions, level of confidence will be indicated. Finally, the local rheumatologist will determine the presence of axial involvement taking all obtained data together (clinical and imaging) – the primary study outcome – and will indicate the level of confidence in that diagnosis [from −5 (definitely not) to + 5 (definitely yes)].

Central assessment of imaging and of the presence of axial involvement. The study will have a central imaging committee consisting of rheumatologists and musculoskeletal radiologists with expertise in PsA and axial SpA, and a separate central clinical committee. Conventional radiographs and MRIs will undergo central blinded review for the presence of changes indicative of axial involvement. Specifically, two primary readers will evaluate radiographs of sacroiliac joints according to the modified New York criteria and will indicate the presence or absence of changes indicative of axial involvement on radiographic assessment of the spine (global evaluation and the presence of sclerosis, erosions, squaring, syndesmophytes, paravertebral ossifications and ankyloses) and on MRI of the sacroiliac joints and spine. For each of the global questions, the level of confidence will be indicated. In a case of discrepancy in global evaluation or if there is a $\geqslant 3$ difference in confidence rating for a global question, the adjudication process by the third reader will be triggered. In addition to the global evaluation, a detailed evaluation of active inflammatory and structural changes on MRI of sacroiliac joints and spine will be performed.

Finally, three members of the central clinical committee will adjudicate for the presence of axial involvement based on the clinical, laboratory and imaging information provided by the

	STUDY PERIOD			
	Pre-Enrolment	**Enrolment**	**Post-Enrolment**	**Close-out**
TIMEPOINT	*Any time before enrolment*	0	Any time after enrolment	After enrolment of all patients
ENROLMENT:				
Eligibility screen	X	X		
Informed consent		X		
INTERVENTIONS:	N/A	N/A	N/A	N/A
ASSESSMENTS:				
1. Clinical assessments				
Demographic characteristics	X	X		
Clinical characteristics and physical examination		X		
Patient reported outcomes		X		
2. Laboratory assessment		X		X (HLA-typing in central lab)
3. Imaging				
Radiography and Magnetic Resonance Imaging		X		
4. Local assessment of the presence of axial involvement		X		
5. Central assessment of the presence of axial involvement				
Central imaging committee			X	
Central clinical committee			X	

Figure 1. Study procedures and time line.

local investigator and the imaging committee. The level of confidence will be indicated.

Study centres will receive a feedback concerning the central judgement and discrepant cases will be discussed during regular meetings.

An overview of the study procedures is presented in Figure 1.

Sample size and study centres

We expect that about 50% of the PsA patients will have axial involvement based on clinical and imaging examinations.[7] With this assumption, the expected sample size needed to estimate the expected frequency of axial involvement with a confidence level of 95% and precision of 5% would be 384.[33] Thus, we plan to include a total of 400 patients with PsA from approximately 50 centres in 20 countries around the world. To obtain a balanced patient population and to avoid potential selection bias, the maximal number of study centres per country will be limited to 5, and the maximal number of patients per study centre will be limited to 20.

Statistical analyses

The frequency of axial involvement in a cohort of patients with PsA according to the local and central assessment will be determined in PsA patients with peripheral involvement (the primary analysis population) as well as in the entire recruited population. The agreement between local and central judgements will be analysed. A subanalysis of the

group without peripheral involvement (i.e. pure axial disease) will also be performed.

The frequency of active inflammatory and structural changes on MRI and radiographs of SIJ and spine suggestive of inflammatory involvement of the axial skeleton in PsA according to the local and central assessments will be calculated. The agreement between local and central judgements on the presence of imaging findings indicative of axial involvement will be analysed for each image type. A sensitivity analysis for geographic and centre-related differences will be performed.

Variables associated with the presence of axial involvement in PsA will be analysed. The diagnostic / classification value of each variable will be evaluated; this will serve as a basis for the development of classification criteria for axial involvement in PsA in a subsequent step.

Genetic data (except HLA-B*27 that will be a part of main assessment) will be analysed exploratorily.

Governance, site monitoring, quality control and data management

The AXIS study will be conducted under the auspices of ASAS and GRAPPA and has been approved by the executive committees of both societies. The study will be coordinated by two Co-Principal Investigators (Co-PIs, DP and DDG) appointed by the executive committees of both societies. The study has a working group consisting of ASAS and GRAPPA members including both Co-PIs and a patient representative plus two young ASAS members supporting the project. The working group appoints members of both central committees.

Study discontinuation

The participants can withdraw their consents to the use of their personal data at any time. This applies to this current study, to the storage of their data and to the use of their data for future research. The study data collected up until the moment the participant withdraws her or his consent will still be used.

Ethical considerations and dissemination

The study will be performed according to the ethical principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. The ethics committee of the coordinating centre of the study located at the Charité University Hospital in Berlin, Germany has approved the conduction of the study (the approval number: EA4/021/21). Thereafter, the study protocol will be approved by the individual Independent Ethics Committee (IEC) / Institutional Review Board (IRB) of participating centres.

The primary study results will be published in an international peer-reviewed journal and will be presented at major international conferences as well at the meetings of both expert societies. The following persons will be eligible for the authorship of the primary result manuscript: members of the working group, members of the central imaging and clinical committees and national coordinators. All investigators contributing at least one patient will be acknowledged as collaborators. Investigators with the largest contribution to the study might be considered for full authorship at the discretion of the working group.

The study is registered at the ClinicalTrials.gov with the ID: NCT04434885.

The completed SPIRIT checklist is available as Supplementary Material.

Acknowledgements

The authors thank all national coordinators, investigators, site personnel and patients participating in the study.

Author contributions

All authors have been involved in designing the study, drafting and/or critically revising the protocol and have approved the final version.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: DP: reports grants and personal fees from AbbVie, Eli Lilly, MSD, Novartis and Pfizer, and personal fees from Bristol Myers Squibb, Roche, UCB, Biocad, GlaxoSmithKline and Gilead. XB: reports grants and personal fees from AbbVie and Novartis, and personal fees BMS, Chugai, Eli Lilly, MSD, Pfizer, UCB, Galapagos and Gilead. FVdB: received speaker and/or consultancy fees from AbbVie, Eli Lilly, Galapagos, Gilead,

Janssen, Novartis, Pfizer and UCB. JB: has received honoraria for talks, advisory boards, paid consultancies and grants for studies from Abbvie (Abbott), Amgen, Baxter, Biogen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, Fresenius, GlaxoSmithKline, Gilead, Hexal, Janssen, Lilly, Medac, MSD (Schering-Plough), Mylan, Mundipharma, Novartis, Pfizer (Wyeth, Hospira), Roche, Sanofi-Aventis and UCB. LCC: reports grant/research support from Abbvie, Amgen, Celgene, Lilly, Novartis, Pfizer and honoraria from Abbvie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Galapagos, Gilead, GSK, Janssen, Lilly, Medac, Novartis, Pfizer and UCB. VC: reports honoraria and/or research grants from Abbvie, Amgen, BMS, Eli Lilly, Janssen, Novartis, Pfizer and UCB, and is supported by a Pfizer Chair Rheumatology Research Award from the Department of Medicine, University of Toronto; spouse is an employee of AstraZeneca. TD: reports personal fees from Novartis Pharma, MSD and Canon MS, outside the submitted work. FAvG: reports grants from Stichting vrienden van Sole Mio, Stichting ASAS, UCB and Novartis and honoraria from Novartis, MSD, Abb Vie and Bristol Myers Squibb. LSG: reports grants and personal fees from UCB and Pfizer, and personal fees from AbbVie, Eli Lilly, Janssen and Novartis. NG: Employed by Abcuro, Inc; stockholder UCB. ABG: received honoraria as an advisory board member and consultant for AnaptsysBio, Avotres Therapeutics, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb Co., Incyte, GSK, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Sun Pharmaceutical Industries, Inc., UCB, Dermavant and Xbiotech. ABG has received research / educational grants from Boehringer Ingelheim, Incyte, Janssen, Novartis, UCB, Xbiotech and Sun Pharma. DvdH: reports personal fees from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda and UCB Pharma, outside the submitted work; and Director of Imaging Rheumatology bv. PSH: received consulting fees (Eli Lilly) and fees for educational services (Pfizer, Novartis, Janssen). KGAH: reports lecture fees from AbbVie, MSD, Pfizer and Novartis. DJ: Although not directly related to this manuscript, DJ has received research grants, educational grants and/or speaker honoraria from AbbVie, Amgen, Biogen, BMS, Celgene, Celltrion, Eli Lilly, Gilead, GSK, Janssen, MSD, Novartis, Pfizer, Roche, Sandoz, Sanofi and UCB. DJ acknowledges that his research time is supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-42001) and Cambridge Arthritis Research Endeavour (CARE). RGL: has acted as a paid consultant for Calyx, CARE Arthritis, IA Group, Novartis and Pfizer. WPM: is Chief Medical Officer of CARE Arthritis Ltd and has acted as a paid consultant/participated in advisory boards for AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer and UCB; received research and/or educational grants from AbbVie, Novartis, Pfizer and UCB; and received speaker fees from AbbVie, Janssen, Novartis, Pfizer and UCB. PM: reports grants and personal fees from AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, Sun and UCB, and personal fees from Boehringer Ingelheim and GlaxoSmithKline. PN: reports consulting / speaker fees from Abbvie, Bristol Myers Squibb, Gilead, Janssen, Novartis, Lilly, Pfizer, Celgene, Roche, Boehringer, Sanofi, Merck, outside the submitted work. FP: reports grants and personal fees from Novartis, Lilly and UCB, and personal fees from AbbVie, AMGEN, BMS, Hexal, MSD, Pfizer and Roche. MP: reports personal fees from Novartis. DDG: Grant support from Abbvie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer and UBC, and consulting fees from Abbvie, Amgen, BMS, Galapagos, Gilead, Eli Lilly, Janssen, Novartis, Pfizer and UCB. JS: has nothing to disclose. MT: has nothing to disclose.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study is supported by unrestricted research grants from AbbVie, Galapagos, Janssen, Lilly, Novartis, Pfizer and UCB.

Patient and public involvement

Patient representative (NG) has been involved in the design of the study and drafting the protocol.

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Supplemental material

Supplemental material for this article is available online.

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