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Review

Celebrating 50 years of spondyloarthritis

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ABSTRACT

It is 50 years since the original spondyloarthritis concept was proposed by Moll and Wright, and in November 2025, rheumatologists (and other health and research professionals in rheumatology and dermatology) gathered in Leeds, the birthplace of spondyloarthritis, to celebrate the milestone. Here, we report on the proceedings of the meeting, which looked back over the last 50 years, noted the current state of the art, and had a look at what might develop in the next 50 years.

INTRODUCTION

In November 2025, a selection of the rheumatology and dermatology healthcare and research community gathered in Leeds to celebrate a remarkable milestone: the 50th Golden Anniversary of Spondyloarthritis research and collaboration. The concept of spondyloarthritis (SpA) was first proposed by Drs Verna Wright and John Moll in a series of articles ranging from 1973 to 1976. The celebration was held at The Queen's Hotel in Leeds from November 2 to 28, 2025, with 100 attendees (Fig 1): the 2-day event honoured 5 decades of scientific discovery, clinical progress, and collaborative partnerships.

The celebrations, jointly arranged by the British Psoriatic Arthritis Consortium and the British Society for Spondyloarthritis, began on Thursday evening with a warm and engaging Celebration Dinner. Prof Philip Helliwell and Prof Helena Marzo-Ortega opened the evening with welcoming remarks and reflections on the history of the concept, including personal memories of working in Leeds since the 1970s. This was followed by an insightful talk from Prof Iain McInnes, who explored how our understanding of SpA pathophysiology has evolved dramatically over the last 50 years, and what the future may hold.

Friday's anniversary meeting showcased an outstanding line-up of experts, each highlighting key milestones and emerging

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Figure 1. Speakers who presented at the Golden Anniversary of Spondyloarthritis meeting, held in Leeds, November 27-28, 2025. From left to right: Iain McInnes, Philip Helliwell, Matt Brown, Helena Marzo-Ortega, Alex Bennett, Laura Coates, Ai Lyn Tan, Stefan Siebert, Oliver FitzGerald, Catherine Smith, and Dirk Elewaut.

directions in SpA research (For the full programme, see online Supplementary material). Presentations covered the evolution of classification criteria, advances in imaging, the role of animal models in shaping scientific understanding, and major developments in genetics. Further sessions focused on axial and peripheral disease, the importance of recognising skin involvement, and the transformation of treatment strategies over time. The meeting concluded with forward-looking discussions on future initiatives and research opportunities, offering an exciting glimpse of what lies ahead.

By bringing together pioneers who shaped the field and innovators who are driving it forward, the Golden Anniversary Meeting proved to be a memorable celebration of progress—and an inspiring foundation for the next chapter in SpA research. Here, we summarise the highlights and key points from the meeting and reflect on the next 50 years for SpA.

Historical aspects

Verna Wright, who died in 1998, arrived in Leeds in the mid-1950s and first published on the association between arthritis and psoriasis in 1956 [1], the publication resulting from his MD thesis at the University of Liverpool [2]. In 1958, he spent a year at Johns Hopkins in Baltimore during which time he continued his study of the clinical association between psoriasis and arthritis. In Leeds, his patients were studied at the Royal Bath Hospital in Harrogate, an old spa hospital, then a regional centre for people with rheumatic complaints, in which patients often spent several months in hospital receiving SpA-like treatments such as mud, massage, exercise, and drinking sulphurated mineral water. Several other publications followed in the late 1950s and 1960s including papers on ankylosing spondylitis, reactive arthritis, and the arthritis associated with inflammatory bowel disease culminating in the concept of 'seronegative spondarthritis' (Fig 2) [3,4], which was supported by the contemporaneous discovery of the association of ankylosing spondylitis with human leukocyte antigen B27 (HLA-B27) [5]. Of course, Wright did not do this by himself: his list of collaborators helping elucidate this concept included Watkinson, Haslock, Macrae, Chamberlain, and Moll, the latter coauthoring and illustrating the definitive textbook [4]. All the work was done using careful clinical observation, deductive reasoning, and plain radiography.

Verna Wright founded the Rheumatism Research Unit at the University of Leeds, which was housed in an old, detached former home on Clarendon Road, in addition to 2 terrace houses just down the road where the biomechanics laboratories were located. He had a small but loyal support team (his infrastructure) who became familiar with all the visiting dignitaries. Verna Wright headed a diverse group in Leeds consisting of 4 divisions: rheumatology, bioengineering, clinical pharmacology, and rehabilitation, each of which was equally productive.

Above all, Wright was a devout Christian. He cofounded the United Beach Mission and spent his summer holidays preaching on the beaches of the UK. He also used to preach on the steps of the Leeds Town Hall on a Tuesday lunchtime. His annual

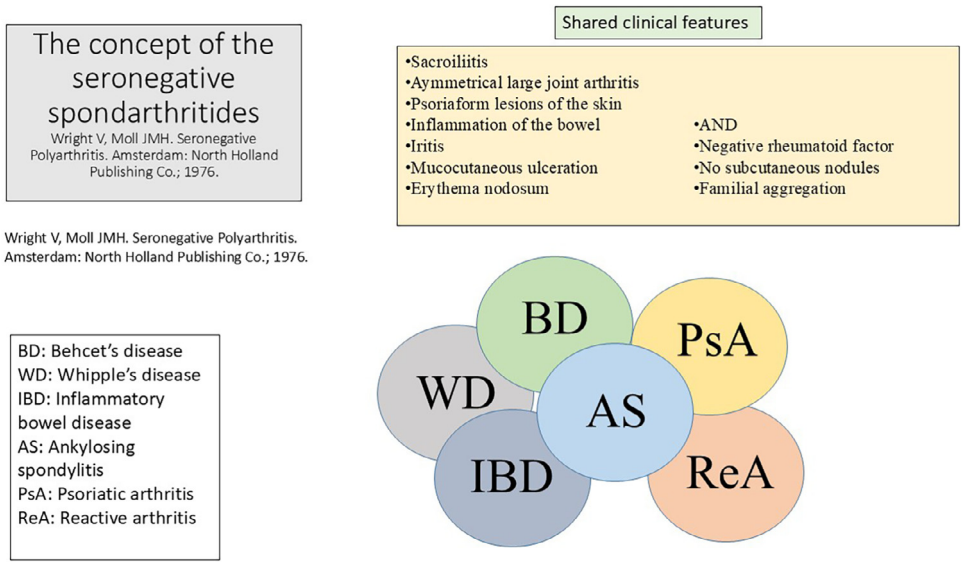

Figure 2. The spondyloarthritis concept (originally termed 'seronegative spondarthritis') as conceived by Verna Wright and John Moll.

'soirees' were an alcohol-free combination of the gospel and exploring the talents of the rheumatology team—many of whom were accomplished performers.

The second era for rheumatology in Leeds started in 1995 with the appointment of Prof Paul Emery to the ARC Chair previously occupied by Verna Wright. At the same time, there were physical changes occurring which provided a radical shift in the way that rheumatology services, and the old Rheumatism Research Unit, were organised and delivered. The Royal Bath Hospital and the Clinical Pharmacology Unit were moved to a rebuilt Chapel Allerton Hospital in Leeds, with a loss of bed numbers and an increase in research accommodation, although the latter was offset by the later closure of the properties in Clarendon Road. With the leadership of Paul Emery, the rheumatology unit grew exponentially: there are now >250 people working in the (newly created) Institute (Leeds Institute of Rheumatic and Musculoskeletal Medicine, a European Centre of Excellence. Spondyloarthritis research continues to be a prominent part with the leadership of Helena Marzo-Ortega and Dennis McGonagle, both of whom ensure that Leeds remains a pioneering centre in this field. Key events in SpA over the last 50 years are summarised in Figure 3.

How concepts of pathophysiology have changed over the last 50 years

Progress in the management of the spondyloarthropathies has been remarkably transformed in the last 2 decades with the advent of pathogenesis-based discovery and the introduction of rational evidence-based treatment algorithms. The treatment of SpA has moved from the application of medications developed for other chronic diseases to those based on primary pathogenesis. Some barriers to progress remain, not least the imperative to appropriate recognition of the variety of immune pathways that are active across discrete target tissues in any 1 patient with multiorgan involvement. It is fallacious to make the assumption that one pathway will dominate in discrete tissues that have by evolutionary imperative developed tissue-specific immune responses for host defence. Looking forward, the field is exciting. We seek evidence that can drive attainment in the clinic of

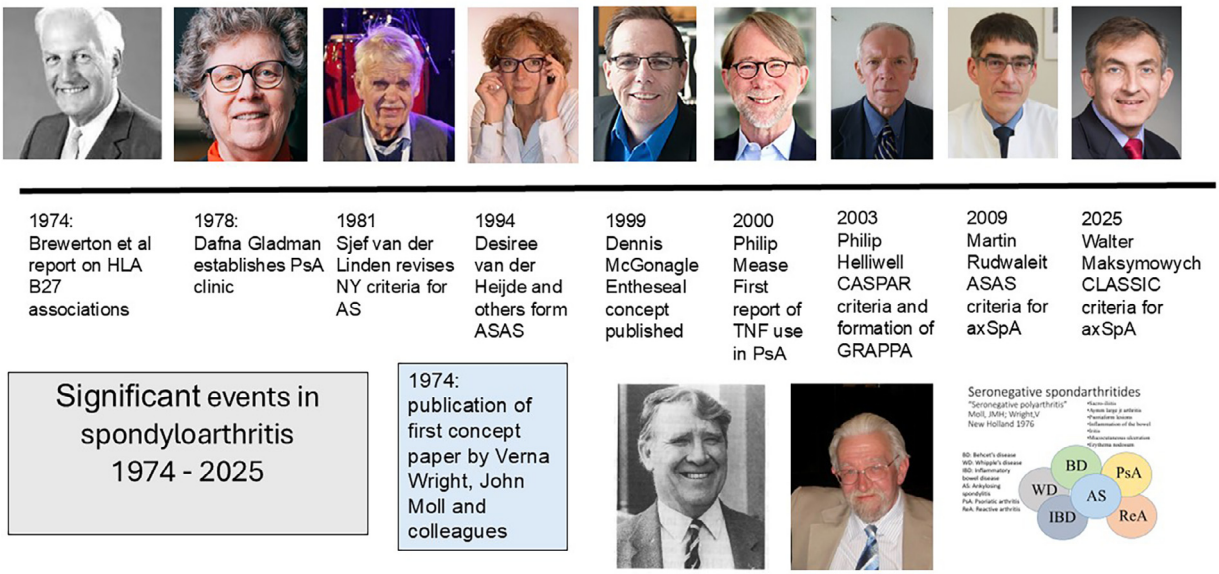

Figure 3. Significant events in spondyloarthritis over the last 50 years.

long-term remission and eventually drug-free remission or cure. Evidence remains sparse in this vital area of research, comprising a so-called evidence-to-aspiration gap. Delivering such ambitions will require a more detailed understanding of molecular tissue pathogenesis, especially to discern those pathways that are of hierarchical dominance. These will likely offer the most therapeutic tractability. In addition, it will be critical to embrace pathogenesis in the context of multimorbidity, which is now the norm in terms of clinical presentation. Finally, a renewed approach to understanding immune disease trajectory will be essential—the SpA conditions may offer the best opportunities in the wider immune disease field to unravel such prodromal molecular events. These challenges are surmountable and offer huge prospects for an even brighter future for the treatment of this spectrum of disorders.

Classification criteria: evolution and impact

The evolution of classification criteria for axial inflammation reflects key milestones in the study of these diseases, including the discovery of the association with HLA B27 and the advent of sensitive 3D imaging such as Magnetic resonance imaging (MRI). In the original New York criteria for ankylosing spondylitis [6], both clinical and radiographic criteria had to be met: the radiographic criterion being at least bilateral grade 2 or unilateral grade 1: today, there still remains debate and difficulty in the inter-rater agreement for the lower grades of involvement (grades 1 and 2) and, indeed, in the definitions using MRI. The revision of the New York criteria by van der Linden et al [7] improved the specificity, but the need to incorporate the peripheral features led to authors broadening the definition to encompass the concept of SpA: of these, the European Spine Study Group became widely adopted [8]. However, in the early 2000s, the Assessment of Spondylitis International Society group collected data to support new classification criteria providing an imaging and a clinical route into classification, and a change of name from ankylosing spondylitis to axial SpA [9]. These criteria were widely adopted. However, ongoing use and evaluation of these criteria led some to doubt their validity across the spectrum of the disease, and, eventually, a new study (CLASSIC), with data collected worldwide, was conceived resulting in revised criteria [10].

In contrast, classification criteria for psoriatic arthritis (PsA) have been relatively unchanged since the publication of the CASPAR criteria in 2006 [11]. The key to CASPAR was a wide international group of collaborators, all experts in the field, and a thorough data-driven approach to analysis. The criteria have served both early and late disease and have been widely adopted and acknowledged [12]. Areas of uncertainty still exist: the 'stem', inflammatory axial disease, arthritis, and enthesitis remain problematic for the nonexpert, and the radiologic criterion reflects the fact that most cases had established articular disease at the time of inclusion. Proposals to include an earlier imaging criterion, such as ultrasound or MRI, have been made but have not yet been validated in the appropriate setting. The classification of axial involvement in PsA has yet to be determined, but results from a large collaborative effort are soon to be published [13].

In summary, classification criteria have evolved over the last 50 years with the accumulation of new knowledge and new methodologies. It is likely that further evolution will occur with advances in imaging, and novel biomarker discovery, in the coming years.

Understanding the pathogenesis of enthesitis in spondyloarthritis through imaging

Enthesitis—the inflammation of tendon, ligament, or joint capsule insertions into bone—is a defining pathological feature of SpA [14]. The term 'enthesitis' was initially described in relation to sports medicine over 6 decades ago [15]. Since then, the interest and publications in this area have continued to increase continually (Fig 4). It is relevant to SpA, which was first described by Ball [16] in 1971. Historically viewed as a focal insertional abnormality, advances in imaging have transformed our understanding of the enthesis and its role in SpA. As illustrated by Prof Michael Benjamin, early anatomical and pathological observations highlighted that the enthesis is not an isolated structure but part of an integrated 'enthesis organ', consisting of fibrocartilage, tendon, and adjacent bone [17–19]. Building on this, Prof Dennis McGonagle described the concept of the synovio-entheseal complex, demonstrated that biomechanical stress at entheses can drive secondary synovial inflammation, providing a unifying framework for SpA pathogenesis [20,21].

Modern imaging modalities—particularly ultrasound and high-resolution MRI—have revealed the full spectrum of entheseal pathology *in vivo* [22,23]. Ultrasound demonstrates structural changes such as tendon thickening, hypoechogenicity, enthesophytes, erosions, and power Doppler signal reflecting active inflammation [24]. MRI provides complementary insights, detecting deep bone marrow oedema, perientheseal soft-tissue inflammation, and the involvement of functional entheses—sites where tendons wrap around bony pulleys without direct attachment [25].

These imaging findings have been instrumental in clarifying the links between enthesitis and clinical manifestations such as psoriatic dactylitis and nail disease [26]. High-resolution MRI has shown that the distal interphalangeal joint, nail bed, and extensor tendon enthesis are anatomically integrated, explaining why nail disease and distal interphalangeal arthritis frequently co-occur in PsA [27,28]. Similarly, imaging of the Achilles tendon enthesis organ has highlighted distinct patterns of inflammation, erosions, and spurs that reflect the biomechanical and immunologic complexity of entheseal pathology [29].

Together, modern imaging techniques have redefined enthesitis as a dynamic, multitissue process central to SpA pathophysiology. These insights not only enhance diagnostic precision but also pave the way for targeted therapeutics and novel outcome measures for clinical trials and routine care.

Historical overview of animal models and how they have changed our view of spondyloarthritis

Although animal models are imperfect, they offer essential translational insights when their strengths and limitations are acknowledged. Early breakthroughs came from HLA-B27 transgenic rats, which demonstrated that overexpression of HLA-B27 can induce a spectrum of SpA-like features, including spondylitis, peripheral arthritis, skin and nail changes, gut inflammation, and orchitis [30]. These findings established a clear link between HLA-B27 and disease whilst raising key questions about underlying mechanisms.

Subsequent tumour necrosis factor (TNF)-driven models, including hTNF and TNF ΔARE mice, confirmed the central role of TNF in sacroiliitis, enthesitis, and chronic ileitis [31,32]. Work on Wnt signalling identified Dickkopf-related protein 1 (DKK-1) as a critical regulator of joint remodelling; its blockade promoted ankylosis, highlighting how inflammation and new

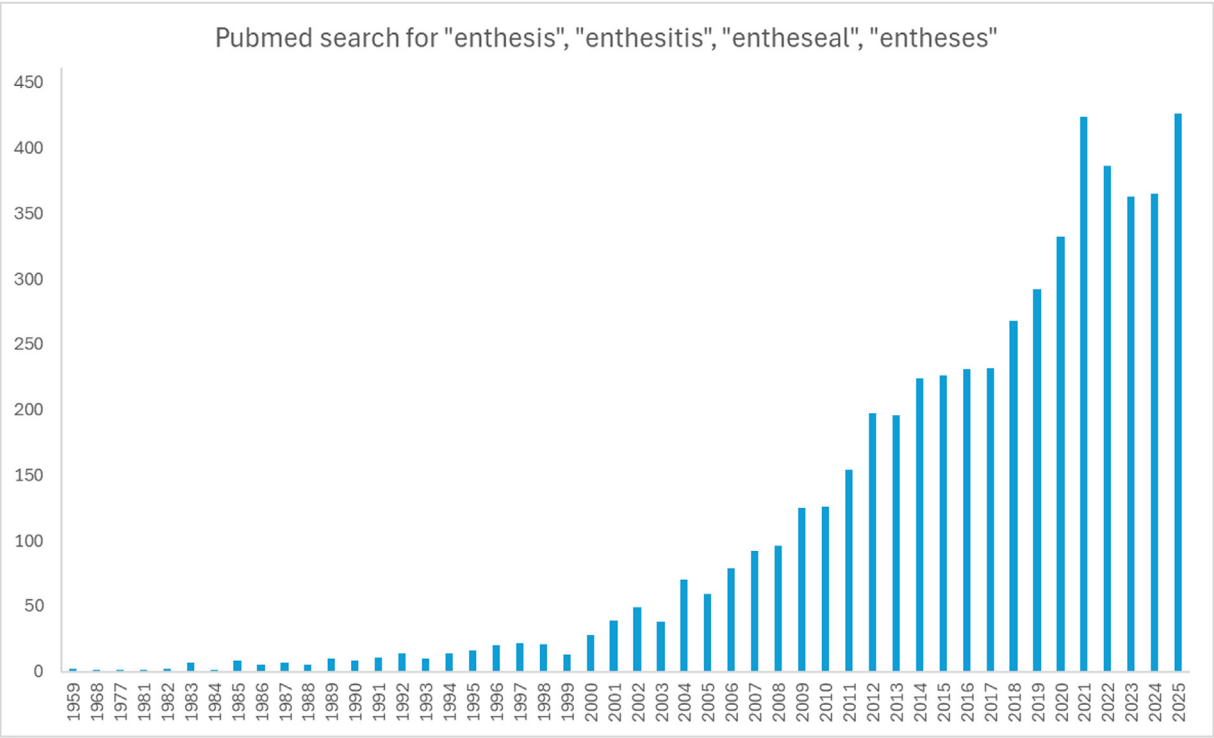

Figure 4. Annual number of PubMed-indexed publications containing the terms 'enthesis', 'enthesitis', 'entheseal,' or 'entheses.' This graph illustrates the progressive increase in scientific output related to enthesis biology and enthesitis from 1956 to 2025, based on PubMed search results for the listed keywords. The steady rise in publications from the late 20th century onward reflects growing recognition of the enthesis as a key anatomical and immunological site in spondyloarthritis. A marked acceleration in research activity is evident from the early 2000s, coinciding with major advances in imaging modalities, the development of the enthesis-organ and synovio-entheseal complex concepts, and increasing interest in enthesitis-driven disease mechanisms. The continuing upward trend highlights the expanding scientific and clinical focus on enthesitis within rheumatology.

bone formation are mechanistically linked yet partially distinct processes.

Beyond TNF, myeloid-specific deletion of A20 (a regulator of NF-κB signalling) led to spontaneous, TNF-independent arthritis and enthesitis [33,34]. This model demonstrated that stromal and myeloid cells can drive pathology and showed responsiveness to JAK inhibition, opening avenues for novel therapeutic strategies. Interleukin 23 (IL-23) overexpression models further implicated $\gamma\delta$ T cells in experimental SpA, although IL-23 may not be the primary driver of axial disease. Macrophage migration inhibitory factor has also emerged as a cytokine linked to structural progression [35]. Further, models have demonstrated that mechanical loading promotes inflammation and erosive disease in mechanosensitive regions, supporting the concept that biomechanical stress contributes to disease localisation [36].

Finally, the microbiome is clearly important in SpA. For example, germ-free conditions protect against gut inflammation in HLA-B27 and TNF models, underscoring the importance of intestinal dysbiosis and barrier dysfunction, though joint disease may persist independently.

Overall, animal models have highlighted several mechanisms and revealed SpA as a multifactorial disease involving genetic predisposition, cytokine networks, stromal–immune interactions, mechanical stress, and environmental triggers, providing greater understanding of this disease.

From HLA-B27 to polygenic risk—the genetics of spondyloarthritis

Genetic studies have transformed our understanding of axial SpA (axSpA), from the landmark discovery of the HLA-B27 association in 1973 to contemporary polygenic and functional genomic analyses. HLA-B27 remains one of the strongest major histocompatibility complex associations observed in any common disease and established axSpA as an immune-mediated condition. Subsequent genome-wide association studies have identified over 100 risk loci, implicating pathways involved in antigen processing, cytokine signalling, mucosal immunity, and epigenetic regulation. Robust gene–gene interaction between HLA class I alleles (HLA-B27 and HLA-B40) and the aminopeptidase ERAP1 in ankylosing spondylitis indicates that these 2 genes closely collaborate in driving disease susceptibility.

Recent large-scale transancestry genome-wide association studies, incorporating more than 25,000 cases and 70,000 controls, have identified 27 new loci and refined causal signals through fine-mapping, transcriptome-wide and proteome-wide association studies. These analyses highlight dysregulation across the IL-23/IL-17 axis, JAK-STAT signalling, and novel pathways including telomere biology. Mucosal immunogenetics has emerged as a key contributor to disease risk, with FUT2 nonsecretor status and ABO blood group A associated with increased susceptibility, likely mediated through effects on the gut microbiome.

Beyond disease susceptibility, genetic coheritability links axSpA risk with inflammatory bowel disease, psoriasis, and osteoporosis. Recent data suggesting that targeting AS-specific expanded CD8 lymphocyte clones is clinically effective suggests a novel approach that may enable the induction of disease remission or its prevention. Looking forward, integrating polygenic risk scores, functional genomics, and immunophenotyping may enable earlier diagnosis and disease interception, shifting axSpA management towards prevention rather than treatment of established disease.

History of imaging and development of new modalities in axial and peripheral disease

Medical imaging has provided crucial insights into SpA, and advances in technology have transformed diagnosis and disease understanding. Original images with X-rays had an early role in detecting structural damage and provided the anchor for identifying and monitoring disease for many decades. More recently, the limitations of X-rays have become more evident —particularly in axial disease with delayed onset of change and poor reliability in grading sacroiliitis. Subsequent developments such as ultrasound, computed tomography (CT), and especially MRI addressed many of these gaps, enabling visualisation of soft tissues and active inflammation. MRI emerged as a pivotal tool in axial SpA, allowing earlier diagnosis, better prognostication, and monitoring of treatment response, whilst also reshaping classification criteria and challenging the historic reliance on radiographic sacroiliitis as an absolute diagnostic requirement.

From the perspective of future developments techniques such as Dixon MRI sequences, whole-body MRI, PET imaging, and quantitative MRI promise greater sensitivity, reproducibility, and objectivity than conventional approaches. In particular, quantitative and AI-assisted imaging—exemplified by the Quantitative Intelligent Inflammation Imaging (Q3I) programme [37] —aims to move reporting from subjective descriptions to precise, measurable assessments of inflammation and disease burden. These advances are positioned as key to improving early detection, understanding pathophysiology, tracking structural progression, and ultimately enhancing clinical decision-making in both axial and peripheral SpA.

Axial involvement in spondyloarthritis—is it uniform or heterogeneous?

Does axial involvement in SpA, particularly in PsA, represent a uniform entity or a heterogeneous spectrum? Data from several cohorts support the idea that axial PsA differs clinically, radiographically, and genetically from axial SpA (axSpA or ankylosing spondylitis), highlighting the complexity of classification and management of axial inflammation across the spectrum of SpA diseases.

Axial disease occurs in approximately 15% to 30% of patients with PsA, although only 2% to 5% present with purely axial manifestations [38]. Most patients have concomitant peripheral involvement. Cohort data, including the AXIS study, demonstrate a prevalence of around 27% axial involvement in biologic-naïve PsA. Notably, up to 35% of PsA patients with axial disease may have isolated spondylitis without sacroiliitis, underscoring differences from classic axSpA.

Phenotypically, axial PsA patients are typically older at presentation, have less inflammatory back pain, and more peripheral arthritis or dactylitis compared with axSpA. Radiographic damage and MRI findings are also distinct. Axial PsA is not primarily HLA-B27 driven: only 30% of axial PsA patients are HLA-B27-positive compared with over 90% in ankylosing spondylitis. However, when present, HLA-B27 appears to modulate disease severity, particularly spinal osteitis. HLA-B27−negative axial PsA often demonstrates milder or normal MRI findings.

Emerging imaging modalities such as whole-body MRI, FDG-PET/CT, and FAPI-PET/CT suggest conventional MRI may underestimate early or soft tissue−predominant inflammation. Enthesitis and extracapsular inflammation appear central to PsA pathophysiology [39]. In normal entheses, IL-23−independent, IL-17−producing $\gamma\delta$ T cells are present, which may explain differential therapeutic responses between IL-17 and IL-23 inhibitors in axSpA. A key research gap remains to define the full spectrum of axial involvement in PsA, including specific imaging features: it is hoped that the AXIS study will fulfil this agenda [40].

Genetically, SpA is highly heritable, but HLA-B27 explains only part of the disease risk. Additional loci and 'genetic load' may influence phenotype severity and comorbidities such as uveitis and inflammatory bowel disease (Fig 5).

Overall, axial PsA demonstrates marked clinical and biological heterogeneity. Current imaging tools are limited, and improved phenotype-genotype stratification is needed to enable personalised treatment strategies within a unifying SpA framework.

The importance of the skin as an impact and treatment domain

Psoriasis has been viewed historically as an epidermal disorder, with messy topicals such as tar and dithranol, in-patient stays, and methotrexate being the main therapeutic options. The serendipitous observation (by rheumatologists) that ciclosporin was effective for psoriasis shifted focus to T cells, and the path towards our current understanding of disease biology relating to skin barrier perturbation, antigen presentation (HLAC-0602), and particularly IL23/17, type 1 interferon, and IL36 signalling. The balance of these pathways influences clinical phenotype: from IL-17 dominant stable plaque disease to IL-36-driven generalised pustular forms. This understanding has driven profound changes in treatment strategies, with effective and largely safe treatments available that directly target these pathways [41].

Psoriasis also exemplifies the importance of understanding causal relationships between health traits—for example, whilst there is strong evidence to support a causal role for adiposity in increasing psoriasis risk and severity (as well as PsA), it is less clear that psoriasis *per se* drives the observed increased risk of cardiovascular disease.

Current clinical challenges include making the right diagnosis, especially in the context of targeted therapies that can trigger 'paradoxical' reactions, and poor response to therapy. Acral site regions are typically poorly responsive, likely related to comparative molecular heterogeneity. Obesity, and related to this, inadequate drug exposure, is another tractable driver of poor response with GLP-1 agonists, alongside proactive therapeutic drug monitoring through model-informed precision dosing showing promise.

Looking to the future, better prediction of individuals at risk of more severe disease, and mechanism-informed early intervention may achieve true disease remission (off drug) and perhaps mitigate risk of disease progression and comorbid burden [42,43]. Future progress will require multidisciplinary collaboration across immune mediated inflammatory disease to optimise research strategy, design, and ultimately—implementation of these advances.

The evolution of treatment strategies over the last 50 years

The treatment of PsA and axSpA has changed radically over the last 50 years, shifting from limited, largely empirical care to a broad, mechanism-based toolkit. Early practice relied on non-steroidal anti-inflammatory drug and, for peripheral arthritis, older DMARD strategies, often with very limited evidence. From the early 2000s onward, choices expanded rapidly with the availability of biologics and oral targeted agents.

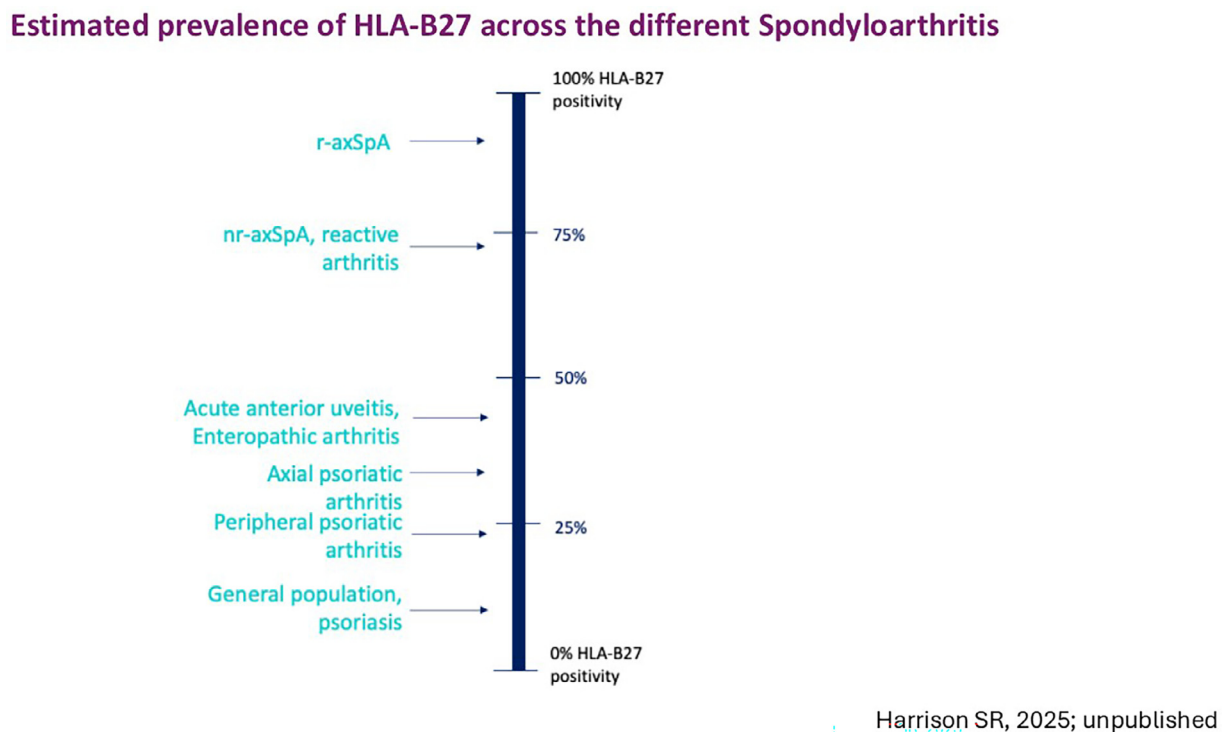

Figure 5. Genetic influences on the phenotype of disease in spondyloarthritis. Spondyloarthritis, in particular axSpA, is highly heritable. Although the strongest genetic risk factor is HLA-B27, it only explains ~20% heritability. Many SNPs have been linked to axSpA but only account for ~5% additional heritability. axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; SNP, single-nucleotide polymorphism.

Importantly, outcomes depend on strategy as well as drug choice. Treat-to-target (T2T) was presented as a key strategy in SpA, using measures such as minimal disease activity or Ankylosing Spondylitis disease activity score. In TICOPA, tight control improved joint and skin responses and increased minimal disease activity attainment versus standard care at 48 weeks, despite limited use of biologics [44]. In contrast, results of the TICOSpA trial (in axSpA) were mixed, with no difference seen in the primary quality of life outcome, but benefits in secondary outcomes like disease activity [45]. Further research into TICOSpA found that implementation was challenging with a significant number of protocol violations and crucially that the majority of patients in usual care were receiving optimal treatment following current treatment recommendations [46].

There are 'windows of opportunity' across the psoriasis-to-PsA transition. Recent studies have confirmed the benefit of early intervention for psoriasis and improved drug-free survival [47]. Many retrospective studies have suggested that patients with psoriasis receiving biologics may have a lower rate of PsA development, but multiple biases in these observational studies are evident [48]. Early-PsA studies (IVEPSA, COMPLETE, GolMePsA, STAMP, SPEED) have tested early combination csDMARDs and early biologic use, with varying results. Some studies have highlighted the benefit of early intensive intervention [49–51], whereas others have shown minimal differences [52,53]. It is likely that differences in exact patient populations and the comparison standard of care treatment arm may influence this.

Ongoing work on precision medicine in PsA, using biomarker-stratified trials like OPTIMISE [54] to match patients to the most effective biologic, will provide important information for clinical practice. Future perspectives include the potential windows of opportunities, personalisation of therapeutic approaches, and personalised medicine using either blood or tissue biomarkers.

New and existing treatments—which to use and when

This review documented the evolution of treatments in PsA, contrasting them with rheumatoid arthritis (RA) and highlighting future directions. RA can be considered as a systemic inflammatory disease in which suppressing central immune pathways effectively controls the disease and therefore prevents joint damage and associated comorbidities. Early-PsA treatment borrowed heavily from this 'rheumatoid thinking', using csDMARDs, steroids, and TNF inhibitors. Although TNF inhibitors proved effective in PsA, the disease pathogenesis is more 'tissue-driven' and cannot be considered simply 'RA with a rash.'

Advances in immunology identified the IL-23/IL-17 axis as central to psoriasis and PsA pathogenesis, leading to disease-specific therapies targeting IL-12/23, IL-23, and IL-17A/F. Over the past 2 decades, multiple biologics and small-molecule inhibitors have expanded therapeutic options, offering increased choice [55]. Trials and clinical experience indicate differences in efficacy across domains (eg, joint and skin responses) and even within drug classes. Safety profiles reflect homeostatic immune functions of the targeted molecules: for example, TNF inhibitors increase bacterial infection, and especially tuberculosis, risk; IL-17 inhibitors are associated with fungal infections and possible inflammatory bowel disease exacerbations; JAK inhibitors raise cardiovascular and viral concerns; and IL-23 inhibitors generally show favourable safety, potentially reflecting their more upstream, regulatory role.

It is important to acknowledge tissue-specific cytokine hierarchies across joints, skin, gut, and entheses, explaining varied clinical responses. PsA heterogeneity exists at molecular, cellular, tissue, and clinical levels, challenging traditional clinical pattern recognition approaches. Furthermore, obesity and metabolic dysfunction are increasingly recognised to be implicated in psoriatic disease pathogenesis, worsening disease activity, and

reducing treatment efficacy, highlighting the importance of holistic thinking and management. Emerging strategies include TYK2 inhibitors, nanobodies, combination biologic therapy, biomarker-guided stratification, and incretin-based metabolic therapies.

Unlike in RA, suppressing systemic inflammation alone is often insufficient in PsA. A deeper understanding of tissue-level immune networks and molecular taxonomy is required. Future trials should be adaptive, biomarker-driven, head-to-head, and focused on prevention and on refractory disease. Despite many therapeutic options, unmet needs remain, and treatment decisions must consider tissues involved, drug mechanisms, safety, and comorbidities.

The future—HIPPOCRATES and ELIPSS

Two large multicentric and well-funded consortia may provide answers to some of the problems highlighted within this review. These include the HIPPOCRATES consortium in Europe and the ELucidating the Landscape of Immunoendotypes in Psoriatic Skin and Synovium (ELLIPSS) consortium in the USA (information provided by Prof Christopher Ritchlin).

HIPPOCRATES and ELLIPSS are both large public-private partnerships addressing unmet needs in Psoriatic Disease. HIPPOCRATES is funded by the EU-based Innovative Medicines Initiative and by industry partners [56], whereas ELLIPSS, part of Accelerating Medicines Partnership-Autoimmune and Immune-Mediated Diseases, is funded by the NIH together with several private partners including industry [57]. The scientific approach being taken by each consortium is nicely complementary. HIPPOCRATES is mainly focused on multiomic analysis and the identification of molecular signatures in peripheral blood samples, whereas ELLIPSS is focused on detailed molecular assessments of diseased tissues, including skin, synovium, and entheses.

For HIPPOCRATES, key achievements to date include the following:

- The establishment of a centralised data management platform where both clinical and molecular data are stored (17 cohorts; >7000 patients to date) and analysed
- The recruitment of >5500 psoriasis patients to the online HIPPOCRATES Prospective Observational Study
- The completion of the first, combined multiomic study addressing progression from psoriasis to PsA
- The identification of candidate biomarkers of progression to PsA and of response to treatment with adalimumab, all requiring validation in large, independent cohorts.

For ELLIPSS, tissue acquisition and analysis using scRNA-seq and spatial transcriptomics is well underway with analysis on >40 skin or synovial tissues to be completed shortly. Additional samples are being collected including baseline and follow-up samples from patients undergoing biologic treatment and psoriasis patients being followed prospectively for the development of PsA.

With both HIPPOCRATES and ELLIPSS, both now past their halfway mark, they are at the 'business-end' with expectations that at least some of the ambitious targets will be achieved. Attention now turns to what questions will need to be addressed post-2027 as even with promising biomarkers or targets being identified, considerable work will be required to ensure that the findings translate into improved patient outcomes.

Summary

This review has highlighted key developments in SpA over the last 50 years. Everyone attending the Golden Anniversary Meeting agreed that Verna Wright would have been delighted with the progress made in SpA. As this meeting highlighted, there have been major advances in classification, imaging, genetics, pathogenesis, and treatment, and there is no doubt that the prospects for patients with SpA have improved markedly. It is worth recollecting that treatment paradigms in the early days were founded on physical, rather than pharmacologic, therapies, and spa hospitals provided protracted in-patient stays. As indicators of the progress made, 2 clinical phenotypes stand out: the infrequency of arthritis mutilans in PsA, and the similar disappearance of patients with complete ankylosis in axial disease. It is clear that there is considerable ongoing investment in these disorders, which holds promise of both prevention and cure: subjects for discussion in future reviews.

Competing interests

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