Referral strategies for early diagnosis of axial spondyloarthritis

Martin Rudwaleit and Joachim Sieper

Abstract | The spectrum of *HLA-B27*-associated inflammatory spine diseases is referred to as axial spondyloarthritis (axSpA). AxSpA encompasses established ankylosing spondylitis (AS) but also nonradiographic axSpA, and can be classified according to the Assessment of SpondyloArthritis international Society classification criteria for axSpA. Specific and effective therapy for axSpA includes education, physiotherapy, NSAIDs and biologic agents, as appropriate. Patients with axSpA, however, are often diagnosed late in the course of the disease. As specific therapy is available, the effective identification of those individuals who are likely to have axSpA among patients with chronic back pain in primary care and their subsequent referral to a rheumatologist for establishing a correct diagnosis is worth pursuing. Candidate referral parameters that can easily be applied to patients with chronic back pain and age at onset ≤45 years (the target population) include inflammatory back pain (IBP) and positivity for *HLA-B27*. Following diagnostic work-up by a rheumatologist, these referral parameters, either alone or in combination, have led to the diagnosis of as many as 33–45% of patients within this target population with axSpA, 41–62% of whom had undiagnosed AS. Thus, educating primary care physicians on the value of IBP and *HLA-B27* testing within this target population, and referral to a rheumatologist if one of these parameters is positive, is a promising approach to reduce the long delay in diagnosing patients with axSpA.

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Introduction

Ankylosing spondylitis (AS) is the prototype subgroup of spondyloarthritis (SpA)—a group of disorders characterized by similar clinical manifestations, a common genetic basis, and similar treatment options.[1,2] Radiographic sacroiliitis has been considered a hallmark of AS and is present in at least 90% of patients with established disease. Radiographic sacroiliitis is also a requirement for the fulfillment of the modified New York criteria for AS established in 1984, which are widely used as classification and diagnostic criteria in clinical practice.[3] Making a diagnosis of AS, however, is often delayed by 6–8 years, mainly because definite evidence of sacroiliitis on plain radiographs is not readily observed during the early stages of disease.[4] Moreover, in early disease the patient's posture does not usually indicate AS. Although chronic low back pain is often the first and predominant symptom of AS, back pain is commonly observed in the general population, and only approximately 5% of individuals with such pain are considered to have AS or axial SpA (axSpA).[5,6] Referral strategies for primary care physicians could, therefore, be useful to channel those patients with chronic back pain who are most likely to have early axSpA to rheumatologists.

Competing interests
M. Rudwaleit declares associations with the following companies: Abbott, Chugai Pharmaceutical Co. (a subsidiary of Roche), MSD, Pfizer and UCB. J. Sieper declares associations with the following companies: Abbott, Bristol–Myers Squibb, Merck, Pfizer, Roche and UCB. See the article online for full details of the relationships.

The concept of axial SpA

MRI has revolutionized the imaging of sacroiliitis. Active inflammation of the sacroiliac joints (SIJ), with or without signs of structural damage, can be accurately visualized by MRI, particularly when plain radiographs of SIJ seem normal or equivocal.[7,8] Sacroiliitis on MRI images, together with clinical manifestations such as inflammatory back pain (IBP), arthritis, enthesitis, uveitis, associated psoriasis or inflammatory bowel disease, response of back pain to NSAIDs, positivity for *HLA-B27* and a positive family history for SpA, have been incorporated into a diagnostic algorithm,[9] a diagnostic probability approach based on likelihood ratios,[4,10] and the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA.[11,12] According to the ASAS criteria, a patient with chronic back pain and age at onset ≤45 years can be classified as having axSpA if sacroiliitis is observed on plain radiographs or, alternatively, by MRI in the presence of at least one further clinical SpA feature (referred to as the imaging arm). Patients can also be classified as having axSpA using a 'clinical arm' in which the patient must be positive for *HLA-B27* and have at least two additional SpA features (Box 1).[12]

The term axSpA has been used to describe the entire spectrum of SpA that has predominant axial involvement, irrespective of the presence of structural damage on plain radiographs.[4] Accordingly, axSpA comprises established AS at one end and an early stage of axSpA (referred to as 'nonradiographic axSpA') at the other end (Figure 1). A substantial proportion of patients with nonradiographic

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Key points

- The long delay of several years in diagnosing ankylosing spondylitis (AS) is unacceptable, as specific therapy is available
- Inflammatory back pain (IBP) is the key clinical symptom of patients with axial spondyloarthritis (axSpA), including AS and nonradiographic axSpA, and is present in 70–80% of patients
- *HLA-B27* is the key laboratory marker of axSpA, present in 70–95% of patients
- Referral programs have focused on patients with chronic back pain, age at onset ≤45 years and presence of at least one further spondyloarthritis parameter, including IBP and/or *HLA-B27*
- In all referral programs, a diagnosis of axSpA was made in 33–45% of referred patients
- Easy-to-apply referral parameters for primary care physicians will contribute to shortening the diagnostic delay in axSpA

Box 1 | ASAS classification criteria for axial SpA*

Sacroiliitis on imaging‡ plus ≥1 SpA feature
Or
HLA-B27 plus ≥2 other SpA features

SpA features:

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease or ulcerative colitis
- Good response to NSAIDs
- Family history of SpA
- *HLA-B27*
- Elevated CRP (in the context of chronic back pain)

*In patients with chronic back pain and age of onset ≤45 years. ‡Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA or definite radiographic sacroiliitis according to modified New York criteria. Abbreviations: ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; SpA, spondyloarthritis. Adapted with permission from the BMJ Group © Rudwaleit, M. *et al. Ann. Rheum. Dis.* **68**, 777–783 (2009).

axSpA will develop AS over time—that is will develop postinflammatory structural damage of the SIJ that can be seen on plain radiographs—but others might have a milder form of nonradiographic axSpA that will not progress. The precise percentage of patients in whom disease progresses from nonradiographic axSpA to AS is currently unknown. In prospective studies of patients with early axSpA, 8–10% developed definite radiographic sacroiliitis after 2 years of follow-up.[13,14] Moreover, a prospective study from the UK revealed that 33% of patients developed radiographic sacroiliitis after an average of 7.7 years,[15] and, in an older study, 59% of patients had progressed after 10 years.[16] The presence of extended active sacroiliitis on MRI images was shown to effectively predict the advancement of disease to the radiographic stage.[15,17] Other potential risk factors for progression include male gender, elevated C-reactive protein (CRP) levels and smoking.[13,18] Although, in the spine, syndesmophytes have the strongest predictive role for further radiographic progression, elevated CRP, male gender and smoking also contribute to progression.[19,20]

Burden of disease

Signs and symptoms, such as presence and degree of IBP, nocturnal pain, morning stiffness, fatigue, frequency of peripheral enthesitis and arthritis, are highly comparable between patients with nonradiographic axSpA and those with early stages of AS. By contrast, CRP concentrations are on average lower in patients with nonradiographic axSpA than in those with AS.[18] Specific and effective therapeutic approaches for axSpA are available: NSAIDs and physiotherapy are the cornerstone of therapy, whereas synthetic DMARDs have no proven efficacy in axial disease.[21] For treatment-resistant active AS anti-TNF agents are approved and form the second step of medical intervention.[21,22] Since 2008, studies have shown that anti-TNF therapy with adalimumab,[23] infliximab,[24] or etanercept[25] is also highly effective in nonradiographic axSpA. In patients with short symptom duration (that is, no more than 3–5 years) and active inflammation, revealed by MRI, remission rates as high as 50% can be achieved during anti-TNF therapy.[24,25] Of note, TNF blockade in AS generally yields greater response rates in younger patients or patients with shorter disease duration, most likely because pain in this patient population is largely caused by inflammation, rather than irreversible mechanical changes that are responsible for discomfort in older patients and those with longer disease duration.[23,26–28] Because of the excellent therapeutic response in early disease, the updated ASAS consensus recommendation on the use of anti-TNF agents in AS and axSpA was extended to patients with nonradiographic axSpA.[22] Clinical trials of these agents in axSpA (including nonradiographic axSpA) are ongoing and we predict that these trials will ultimately lead to the approval of anti-TNF agents not only for AS but for the entire spectrum of axSpA.

Epidemiology of AS and axSpA

The prevalence of AS has been reported from population studies to be between 0.1% and 1.4%.[29–37] A study of *HLA-B27* positive and negative blood donors from Germany estimated a prevalence of AS of 0.66%, taking into account the male to female ratio in AS of 2–3:1.[32,33] The incidence rate of AS has been reported to be ~7.3 per 100,000 adults in the USA, 6.9 per 100,000 adults in Finland, and 7.3 per 100,000 in Norway; these rates have remained stable over the past 50 years.[29,34] The incidence and prevalence of AS generally mirrors the frequency of *HLA-B27* in the population, which explains the virtual absence of AS in Southern Africa, low rates of AS in Japan, higher rates in Norway as compared with other European countries, and very high rates among the native people of circumpolar arctic and subarctic regions of Eurasia and North America.[34] The prevalence of all SpA subtypes in North America, Germany, France, Greece, Lithuania and China are estimated to be 0.3–1.9%, and are, therefore, at least as high as those reported for rheumatoid arthritis.[31–36]

Within SpA, AS and undifferentiated SpA are the most common subtypes.[31,32] Studies have shown that approximately 50–70% of patients with undifferentiated SpA have IBP and can likely be classified as having axSpA, yet the prevalence of axSpA among patients with chronic back pain is less well studied. A study from the UK conducted among a four-partner general practice over a period of 1 year estimated that axSpA had a prevalence of 5% among

313 patients with back pain—a figure that is often cited.[5] In 2009, a large population study from China reported a prevalence of chronic back pain of 7.2% (787 of 10,921) and 11.7% of those with chronic back pain were diagnosed with axSpA after rheumatological examination.[31] The absolute prevalence of axSpA in China was estimated to be 0.80% (0.25% AS and 0.55% nonradiographic axSpA).[31] Data from three studies that included patients with newly diagnosed axSpA revealed that 38%, 50% and 70% of patients were classified as having nonradiographic axSpA and 62%, 50%, and 30%, as having AS, respectively.[12,37,38] The respective mean duration of back pain in these studies was 8.4, 7.7, and 6.1 years, respectively, underlining the importance of disease duration for the evolution of nonradiographic axSpA to AS.[12,37,38]

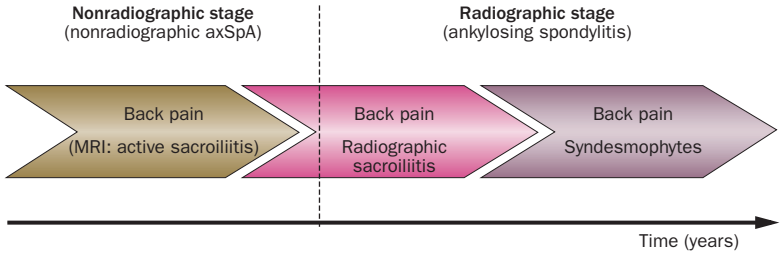

Figure 1 | The concept of axSpA. It should be noted that not all patients will evolve from the nonradiographic axSpA stage to the radiographic stage. Predictors of progression include disease duration (time), severity and extent of MRI inflammation, male gender and other, yet unknown, factors. Abbreviation: axSpA, axial spondyloarthritis. Adapted with permission from John Wiley & Sons, Inc. © Rudwaleit, M., Khan, M. A. & Sieper, J. *Arthritis Rheum.* **52**, 1000–1008 (2005).

Referral strategies for axSpA

Target population

Back pain is a common health problem in many populations. Both AS and axSpA are characterized by chronic back pain and a young age at onset. In AS, disease onset is usually in the third decade of life and by the age of 45 years ≥95% of patients are symptomatic.[39] Thus, the target population for which axSpA is a relevant differential diagnosis are patients with chronic back pain (>3 months) and age at onset of ≤45 years.[4,9] These two parameters also form the entry criterion for the ASAS classification of axSpA.[12]

Candidate referral parameters for axSpA

In the target population, further parameters are needed to reduce the number of patients who do not have axSpA referred to a rheumatologist. Suitable referral parameters should have a high sensitivity, that is, are frequently present in patients with axSpA and so capture the majority of patients, but also have a reasonable specificity.[40] Given these requirements, suitable referral parameters in SpA would be IBP, a good response of back pain to NSAIDs, *HLA-B27* positivity, and an MRI showing damaged or inflamed SIJ (Table 1). Cost and feasibility of referral parameters, however, also require consideration. Characterizing the clinical symptom of IBP does not have any associated costs, is relatively easy to assess, but does require the clinician to have some relevant experience. *HLA-B27* testing incurs a single moderate cost but provides a clear result (that is, positive or negative). Owing to high costs and limited availability, MRI is not a suitable referral parameter; interpretation of MRI images can also be difficult. A good response to NSAIDs is a useful diagnostic test in axSpA,[4,9,41] but might lead to selective referral of patients who are good responders if used as a routine referral parameter.

Inflammatory back pain

IBP in patients with AS results from inflammation of the SIJ and/or spine and is associated with certain characteristics including morning stiffness, improvement of back pain with exercise but no improvement with rest, night pain and/or pain in the early morning, insidious onset, and alternating buttock pain. Calin *et al.*[42] published the first set of criteria for IBP to be used as a screening test for AS. Thereafter, two other sets of criteria for screening for IBP were developed.[43,44] In all IBP criteria sets, a combination of features usually perform better than a single one. Slight differences in sensitivity and specificity of the IBP criteria sets were reported in the original studies.[42–44] However, on the basis of the available data it is difficult to claim that one set of criteria is superior to the others. In an ASAS valdiation study,[12] no difference was found with respect to final diagnosis in the performance of the three sets of IBP criteria. Moreover, all IBP criteria sets perform reasonably well in daily clinical practice, yet the Calin criteria are frequently used in this setting.

Proposed strategies for axSpA

We hypothesized that referral of patients from the target population who have at least one SpA referral parameter (such as IBP or positivity for *HLA-B27*) to rheumatologists might be effective in identifying and diagnosing patients with axSpA.[40] For the clinical symptom IBP (assumed prevalence of 5% of axSpA among patients with chronic back pain, sensitivity 75%, specificity 76%), an estimated seven patients would need to be referred to a rheumatologist to diagnose axSpA in one patient.[40] By contrast, if a patient of the target population is referred because of a positive test for *HLA-B27* (which has a sensitivity of 90%, specificity 90%) it was calculated that one-third of referred patients will be diagnosed as having axSpA (Figure 2, Table 1).[40] This referral proposal was then tested in prospective field studies.

Testing axSpA referral strategies

Monocenter studies

The first study to test our proposed referral strategy was a single-center study conducted in Berlin, Germany, and surrounding areas (Table 2).[37] Orthopedists and general practitioners were invited to refer patients of the target population who had no clear back pain diagnosis if either IBP was present or if the patient was *HLA-B27* positive. To keep the assessment of IBP simple, the fulfillment of formal IBP criteria was not required. Rather, physicians were informed about the most important IBP features: morning stiffness >30 minutes, pain at night and/or early morning and improvement of pain with exercise. However, fulfillment of one, two or all three of these

Table 1 | Comparison of clinical and laboratory SpA features relevant for axial SpA

Parameter	Sensitivity* %	Specificity* %	Sensitivity % (best representative estimate)	Specificity % (best representative estimate)	Positive likelihood ratio‡
Inflammatory back pain	38–95	76–100	75	76	3.1
Heel pain (enthesitis)	16–52	89–96	37	89	3.4
Peripheral arthritis	26–62	91–100	40	90	4.0
Dactylitis	12–27	96–99	18	96	4.5
Anterior uveitis	10–22	97–100	22	97	7.3
Psoriasis	1–17	96	10	96	2.5
IBD	2–7	99	4	99	4.0
Positive family history for AS, reactive arthritis, IBD, psoriasis, anterior uveitis	7–36	93–100	32	95	6.4
Response to NSAIDs	64–77	75–85	77	85	5.1
Elevated acute phase reactants (CRP)	38–69	67–100	50	80	2.5
HLA-B27	83–96	91–96	90	90§	9.0
MRI of sacroiliac joints	54–93	83–100	90‖	90‖	9.0

*For the details of the primary literature please refer to Supplementary reference list (Supplementary Table 1 online). ‡Positive likelihood ratio refers to sensitivity/(1-specificity); in most Western European populations this ratio ranges between 5–10%, corresponding to a specificity of 90–95%. §The specificity figure depends on the background prevalence in the population. ‖No gold standard is available to assess the true sensitivity of sacroiliitis on MRI in axial SpA. The reported specificities depend largely on type of control group, technical performance, and interpretation of MRI findings. Abbreviations: AS, ankylosing spondylitis; CRP, C-reactive protein; IBD, inflammatory bowel disease; SpA, spondyloarthritis. Adapted with permission from the BMJ Group © Rudwaleit, M. *et al*. *Ann. Rheum. Dis.* **63**, 535–543 (2004).

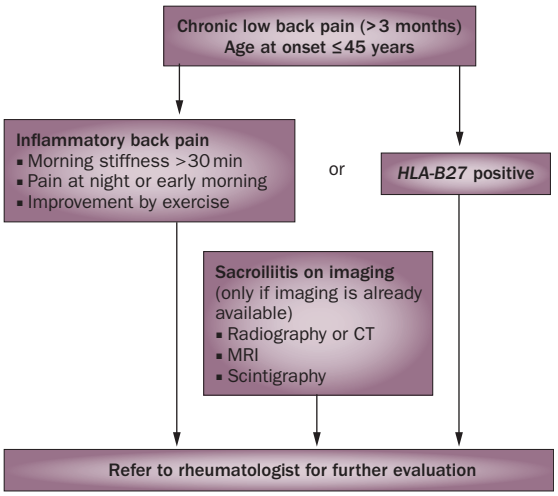

Figure 2 | Proposed referral strategy for axial spondyloarthritis for primary care physicians. Patients who present with chronic low back pain and age of onset ≤45 years can be sent to a rheumatologist for assessment if they have inflammatory back pain or are *HLA-B27* positive. Adapted with permission from the BMJ Group © Sieper, J. & Rudwaleit, M. *Ann. Rheum. Dis*. **64**, 659–663 (2009).

features was not required. As imaging of SIJ is sometimes performed in primary care, physicians could also refer patients of the target population if sacroiliitis was indicated by any already available imaging modality (including radiography, CT, scintigraphy and MRI), but the ordering of such imaging tests was not encouraged.

Overall, 350 patients of the target population were referred and a diagnosis of axSpA was made in 45.4%. AxSpA was diagnosed in 34.2% who were referred using a single parameter, but this value increased to 62.6% of patients who met at least two referral parameters. If IBP was the only referral parameter, axSpA was diagnosed in 27% of patients, and if *HLA-B27* was the only parameter, axSpA was diagnosed in 46%. Suspected sacroiliitis on imaging as the only referral parameter yielded a diagnosis of axSpA in only 26% of patients. Among the patients diagnosed with axSpA, 50.3% were classified as having AS and 49.7% nonradiographic axSpA.[37] This first proof-of-concept study therefore confirmed that a referral strategy can be effective. The study also confirmed the expected superiority of *HLA-B27* testing over IBP regarding the yield of diagnosis of axSpA: 1 in 3.7 patients referred with IBP, and 1 in 2.1 patients with a positive *HLA-B27* test were diagnosed with axSpA. The overall higher than expected rate of positive diagnoses in this study might reflect preselection of patients by the referring physicians, in that patients in whom SpA was already strongly considered, but not diagnosed, were presumably preferentially referred.

In a second small study from Austria,[45] 345 general practitioners received a folder explaining the Calin criteria for IBP and were asked to refer patients younger than 45 years who fulfilled the criteria. Of 92 referred patients, a diagnosis of SpA was made in 30 (33%). Neck pain and reduced cervical spine sagittal movement was negatively associated with SpA, whereas *HLA-B27* positivity and an elevated CRP level contributed to a diagnosis of axSpA.[45]

National multicenter study

In a national multicenter study coordinated in Germany,[38] we aimed to confirm the data from the monocenter study[37] in a broader setting (Table 2). This study, referred to as MASTER (multicentre AS survey trial to evaluate and compare referral parameters in early SpA) included 259 physicians across the country who referred patients to 43 rheumatologists in private practices and hospitals.

Table 2 | Overview of studies evaluating referral strategies for patients with chronic back pain and age at onset <45 years

Study	Referred patients (*n*)	Referral strategy	Proportion of referred patients diagnosed with axSpA (%)	Proportion of axSpA diagnosed with nonradiographic axSpA (%)	Proportion of axSpA diagnosed with AS (%)
Monocenter studies					
Germany Brandt *et al.* (2007)[37]	350	IBP or *HLA-B27* positivity (or sacroiliitis on imaging)	45.4	49.7	50.3
Austria Hermann *et al.* (2009)[45]	92	IBP (according to Calin criteria)	33.0	46.7	53.3
Multicenter studies					
Germany (MASTER) Poddubnyy *et al.* (2011)[38]	318 (strategy 1) 242 (strategy 2)	IBP or *HLA-B27* positivity (or sacroiliitis on imaging) At least two out of five features: IBP, *HLA-B27* positivity, sacroiliitis on imaging, good response to NSAIDs, positive family history	41.8 36.8	38.4 38.2	61.6 61.8
Germany Braun *et al.* (2011)[46]	322	IBP and/or good response to NSAIDs according to a computer algorithm	35.1	58.4	41.6
International study (RADAR) Sieper *et al.* (2011)[47]	504 (strategy 1) 568 (strategy 2)	IBP or *HLA-B27* positivity (or sacroiliitis on imaging) At least two out of six features: IBP, *HLA-B27* positivity, sacroiliitis on imaging, good response to NSAIDs, positive family history, extra-articular manifestations	35.6 39.8	NA NA	NA NA

Abbreviations: AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; IBP, inflammatory back pain; NA, not applicable.

Physicians were randomly allocated to refer patients according to two different strategies.[38] Referral by strategy 1 was the same as in the monocenter study from Berlin, that is, IBP, positive *HLA-B27* test or suspicion of sacroiliitis on imaging (if available). In addition, an alternative strategy (strategy 2) was tested in an exploratory way, in which physicians were asked to refer patients from the target population only if at least two SpA parameters were present: IBP, *HLA-B27*, suspicion of sacroiliitis by imaging (if available), a positive family history of AS and/or SpA, or a good response to NSAIDs; patients with other SpA parameters (such as uveitis) could also be referred.

In total, 560 patients were referred, 318 patients according to strategy 1 (57%) and 242 patients by strategy 2 (43%). Of the patients referred by the criteria in strategy 1, 41.8% were diagnosed with axSpA, which was similar to the figure of 45.4% obtained in the monocenter study. In strategy 1, 38.4% of patients were referred with one referral parameter but 61.6% had two or more parameters. The most frequent referral parameter was IBP (76.7% of cases). Among patients with IBP (alone or in combination with another referral parameter), a diagnosis of axSpA was made in 41.8%; if IBP was the only referral parameter, axSpA was diagnosed in 16.2%. Positivity for *HLA-B27* alone or in combination with other criteria (44.7% of referred patients) yielded a diagnosis of axSpA in 57.7%, and sacroiliitis alone or in combination with other parameters (55.7% of referred patients) yielded a diagnosis of axSpA in 50.3%. By contrast, among patients referred by strategy 2, a diagnosis of axSpA was made in 36.8% of patients. The most frequent referral parameters were IBP (87.6%) and a good response to NSAIDs (64.4%), followed by a positive *HLA-B27* test (52.2%), sacroiliitis on imaging (38.0%), and a positive family history (19.0%). Thus, the effectiveness of referral strategy 1 was confirmed in a multicenter setting. Moreover, the more complicated referral strategy did not increase the rate of a positive diagnosis, and therefore, does not seem to be superior to the simpler strategy.[38]

Another national multicenter study involved 322 patients referred by 143 physicians and diagnosed by 36 rheumatologists (Table 2).[46] A diagnosis of axSpA was made in 35% of referred patients. In this study, patients were referred if IBP or a good response to NSAIDs were present. The decision to refer patients, however, was made according to a computer algorithm not by the presence or absence of IBP as judged by the physician. As a result of this specific study design, an educational effect on the referring physician regarding IBP seems less evident. The study confirmed that a diagnosis of axSpA was more likely if more features of IBP were present and/or the patients responded to NSAIDs.[46]

International multicenter study

Referral strategies 1 and 2 (same as described in the multicenter study above, except that strategy 2 had the addition of extra-articular manifestations to the list of referral parameters) were further tested in an international study (RADAR) involving physicians and rheumatologists in

16 countries and 1072 patients, the results of which are not yet fully published (Table 2).[47] A diagnosis of axSpA was made in 35.6% (strategy 1) and 39.8% (strategy 2) of referred patients, respectively, with IBP being the most frequently used referral parameter across the strategies (93–96%). In contrast to MASTER,[38] suspected sacroiliitis on imaging was used in clinical practice more frequently (27.2% and 35.9% in strategy 1 and strategy 2, respectively) than *HLA-B27* testing (17.3% and 17.1% in strategy 1 and strategy 2, respectively).[47] Similar to MASTER,[38] however, a more complicated referral strategy had no obvious advantage when compared with requirement for only one SpA parameter, that is IBP or a positive *HLA-B27* test.[47]

Other studies related to referral

A study from Norfolk, UK, assessed the knowledge of general practitioners regarding AS and/or axSpA and IBP using a postal questionnaire.[48] Not surprisingly, this survey revealed inconsistencies in the understanding of the diagnosis and management of AS, including the assessment of IBP. Despite these inconsistencies and limitations, 78% of general practitioners could identify at least 50% of features relevant for IBP. Although this figure is promising, it underlines the need for continuing medical education on axSpA and IBP to establish successful referral programs in primary care. A study from the USA developed a comprehensive diagnostic tool to identify undiagnosed AS rather than early axSpA. To date, this tool has been tested in a cohort of patients with AS but not in primary care.[49]

The value of referral programs

The objective of referral programs in axSpA is to identify patients with possible axSpA early, make a correct diagnosis, and to provide the best possible care as early as possible. The most effective care includes appropriate education, physical exercise, and medical therapy (including NSAIDs and anti-TNF agents) as needed. An early and correct diagnosis of axSpA avoids unnecessary diagnostic and therapeutic interventions in patients with chronic back pain and reassures the patient about the nature of their complaints. Across the referral studies, 41–62% of patients diagnosed with axSpA actually had AS (average symptom duration 9–10 years), a diagnosis that was possibly suspected but remained undiagnosed. Thus, appropriate management for these hitherto undiagnosed patients became feasible owing to the referral programs.

If referral programs are effectively put into practice, one can anticipate that in the future patients with nonradiographic axSpA, as well as those with undiagnosed AS, might be diagnosed more frequently. Definite sacroiliitis as seen on plain radiographs requires years to develop; the shorter the time from onset of symptoms to diagnosis, the more patients will be diagnosed with nonradiographic axSpA rather than AS.[15–18] Promisingly, the median duration of back pain in patients diagnosed as axSpA in the referral studies was rather short: 3.3 years in the Austrian study;[45] and 2 years (mean 4.6 years) in patients diagnosed as nonradiographic axSpA in the German monocenter study, 30% of whom had a symptom duration of less than 1 year.[37] Although whether early treatment slows the progression from nonradiographic axSpA to established AS is currently unknown, the appropriate treatment of signs and symptoms and restoration of physical function might be of equal or even greater importance to the patient.[50]

Conclusion

Patients with axSpA at the nonradiographic axSpA stage can be reliably diagnosed early, prior to the development of AS, and can be classified by use of the ASAS classification criteria for axSpA. Testing patients with chronic back pain and age at onset of ≤45years in primary care for the presence of IBP or *HLA-B27*, followed by referral to a rheumatologist, has been proven effective in monocenter and multicenter referral studies in identifying patients with axSpA among the large number of patients with chronic back pain. In these studies, 33–45% of referred patients were found to have axSpA, implicating that one-third of patients who are referred according to the referral strategy will have a diagnosis of axSpA. In fact, many of these patients had in fact undiagnosed AS for a number of years. An earlier diagnosis as a result of structured referral programs enables the most appropriate care of back pain and other symptoms in patients with axSpA and is likely to reduce the long diagnostic delay of up to 10 years, which is still reality in AS. Educating primary care physicians about the value of IBP and *HLA-B27* is, therefore, worthwhile.

Review criteria

Papers included in this Review were identified by searches of the PubMed database until November 2011 using the following terms: "ankylosing spondylitis"; "spondyloarthritis"; "spondylarthropathy" in combination with "diagnosis"; "classification criteria"; "epidemiology"; "prevalence"; "incidence", "screening" and "referral".

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Author contributions

M. Rudwaleit and J. Sieper researched data for the article and substantially contributed to the discussion of content. M. Rudwaleit also wrote the article and edited the manuscript prior to submission.

Supplementary information

Supplementary information is linked to the online version of the paper at www.nature.com/nrrheum