Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis

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ABSTRACT

The aim of this work was to develop a consensual recommendation under the auspices of the Assessment of SpondyloArthritis international Society (ASAS) for early referral of patients with a suspicion of axial spondyloarthritis by non-rheumatologists. The development of a referral recommendation consisted of four phases: (1) systematic literature review, (2) the first Delphi round aiming at identification of unmet needs and development of a candidate list of referral parameters, (3) the second Delphi round aiming at identification of the most useful combination of referral parameters and (4) final discussion and formal endorsement by ASAS membership. The following consensus on a referral recommendation was achieved as a result of the Delphi processes and final voting: “Patients with chronic back pain (duration ≥3 months) and back pain onset before 45 years of age should be referred to a rheumatologist if at least one of the following parameters is present: Inflammatory back pain; human leucocyte antigen-B27; Sacroiliitis on imaging if available (X-rays or magnetic resonance imaging); Peripheral manifestations (arthritis, enthesitis, dactylitis); Extra-articular manifestations (psoriasis, inflammatory bowel disease, uveitis); Positive family history for spondyloarthritis; Good response to non-steroidal anti-inflammatory drugs; Elevated acute phase reactant.” A consensual ASAS-endorsed referral recommendation for patients suspected of having axial spondyloarthritis was developed as a flexible and universal strategy to be used in clinical practice by primary care physicians or non-rheumatology specialists. The practical value of this strategy applied in different settings should be determined in future studies.

There is still a substantial gap of 5–8 years between the onset of symptoms and the diagnosis of axial spondyloarthritis (axSpA).1–3 One of the major reasons for such a delay is a late referral of patients to a rheumatologist by general practitioners and other physicians encountering patients with back pain. This late referral can be caused by the referring doctor and/or by the patient. The leading clinical manifestation of axSpA is chronic back pain. However, chronic back pain is highly prevalent in the general population and axSpA is responsible for only about 5% of the cases.4 Obviously, it is not feasible to refer all patients with chronic back pain to a rheumatologist with such a relatively low prevalence of axSpA among chronic back pain patients. A certain kind of a “filter” based on the presence of features characteristic of axSpA is necessary in order to sufficiently increase the likelihood of axSpA in patients referred to a rheumatologist by non-rheumatologists (ie, general practitioners, orthopaedic surgeons, gastroenterologists, dermatologists). At the same time, such a ‘filter’ (further called ‘referral strategy’) should not be too complex in order to make its application feasible by all type of doctors. While several referral strategies2,3,5-9 have been proposed and tested over the last 10 years, to date a universally accepted referral strategy is still lacking. In this work, we aim to summarise existing data concerning referral strategies for patients suspected of having axSpA and to develop a consensual Assessment of SpondyloArthritis international Society (ASAS)-endorsed recommendation for early referral of this group.

METHODS

Development of the ASAS-endorsed referral recommendations for patients suspected of having axial SpA by primary care physicians or non-rheumatology specialists consisted of the following four phases: (1) systematic literature review (SLR); (2) the first Delphi round aiming at identification of unmet needs, subsequent discussion at the ASAS annual meeting in 2013, and development of the referral parameter candidate list; (3) the second Delphi round aiming at identification of the most useful combination of the referral parameters and (4) discussion on a final proposal for the recommendations and voting for endorsement at the ASAS annual meeting in 2014.

Systematic literature review

The main research question guiding the systematic literature search was, “What is the optimal referral strategy for identification of patients with axSpA?”. Specifically, we were interested in how frequently axSpA is diagnosed in patients referred to a rheumatologist using a referral strategy and what the yield is of individual screening parameters in identifying axSpA. A systematic literature search was performed in MEDLINE (OVID), EMBASE (OVID) and Cochrane Central in December 2012. The search strategy consisted of a combination of text words and controlled vocabulary terms (eg, MeSH terms) related to spondyloarthritis, referral and screening. No limitations were applied. One reviewer (AW) screened titles and abstracts on eligibility for inclusion, after which full text was read by the reviewer. Additionally, references of
included papers and abstracts from American College of Rheumatology and European League Against Rheumatism 2011 and 2012 meetings were hand searched. Finally, the authors of this paper could add references that were not retrieved by the SLR.

The first Delphi round
This round was conducted by means of an online survey between December 2012 and January 2013. In this survey, ASAS members were asked to answer questions concerning the need for referral recommendations in general, the possible structure of such a recommendation set, the number of referral parameters to be included and the most relevant candidate parameters that should be included in a referral strategy.

At the ASAS annual meeting in Houston, USA, in January 2013, the results of the SLR and survey were presented and discussed. Subsequently, the most likely candidates for the referral parameters were identified and proposals for subsets of a referral recommendation were developed.

The second Delphi round
The second Delphi round was conducted by means of an online survey between December 2013 and January 2014. In this round, ASAS members could express their opinion on different constructs of a possible consensual referral recommendation and referral parameters to be included.

Final discussion and final voting
At the ASAS annual meeting in Dusseldorf, Germany, in January 2014, a comprehensive overview of the previous rounds was given, including an update of the SLR, followed by a discussion and final voting on a consensual recommendation on referral.

RESULTS
Summary of the SLR
Figure 1 shows the results of the SLR. In total, six full-text papers and two abstracts were included.

The studies were conducted in different countries and evaluated in total 10 referral strategies of which some were tested against each other (table 1). Patients could be referred by general practitioners, orthopaedic surgeons and other physicians. All strategies required that the back pain is chronic (at least three months) and had an age of onset ≤45 years. One study did not apply any other criteria for referral, whereas in other studies one or more referral parameters were required, for example, an inflammatory character of the chronic back pain or the presence of human leucocyte antigen (HLA)-B27.

In total, 3014 patients were referred, of which 47.3% were men (range 33–55%, unknown in one abstract) with a mean age of 36.7 years (range 31–40 years, unknown in one abstract), mean symptom duration of 6.1 years (range 1.1–8.7 years, unknown in five papers/abstracts) and mean 45.6% were HLA-B27 positive (range 34–61%, unknown in two abstracts).

Considering full-text papers only, axSpA was diagnosed on average in 38.6% of the referred patients (range 32.6–45.4%). Patients were frequently referred with a combination of parameters being present. In those patients who had inflammatory back pain (IBP) among the combination of referral parameters, on average 43% had axSpA (range 35–56%, n=5 studies). When HLA-B27 was included in a combination, on average 62% (range 49–72%, n=5 studies) of the patients had axSpA; with sacroiliitis on imaging in the combination, this was 63% (range 50–75%, n=5 studies); with response to non-steroidal anti-inflammatory drugs (NSAIDs) 36% (range 35–38%, n=2 studies); with a positive family history for SpA 43% (range 40–46%, n=2 studies); and with the presence of extra-articular manifestations 56% (n=1 study) of the patients had axSpA.

The agreement between the referring physician and the rheumatologists was poor with regard to IBP (kappa values of 0.04–0.20) and with regard to response to NSAIDs (kappa value of 0.21). Kappa statistics were not available for the other referral parameters.

Some studies reported the positive likelihood ratios of individual referral parameters regarding the presence of axSpA. The positive likelihood ratio for IBP was 1.3–1.7, for HLA-B27 3.3, for sacroiliitis on imaging 19.9, for the presence of extra-articular manifestations 2.2, for a positive family history for SpA 1.5 and for response to NSAIDs 1.4 (all n=1 study, except for IBP n=2 studies).

The first Delphi round
A total number of 106 full and 30 associate ASAS members were invited to participate in the survey, of whom 87 full members (82%) and 22 associate members (73%) have responded. The majority of the ASAS members indicated that there is a clear need for referral recommendations; application of a certain strategy for referral to a rheumatologist was considered to be necessary by 90% of the ASAS members, and 93% were in favour of the development of a referral recommendation under the auspices of ASAS. There was an overall consensus that the referral recommendation should be easy to apply and include a limited number of parameters.

The survey allowed the development of preferred candidate parameters for the inclusion in such a recommendation set (on the background of the presence of chronic back pain, ie, 3 months and longer). The most frequently mentioned candidate parameters were IBP, age of onset back pain before 43 years of age, HLA-B27 positivity and sacroiliitis on imaging (only if available) (online supplementary figure S1). However, the importance of other SpA parameters such as extra-articular manifestations (psoriasis, uveitis, inflammatory bowel disease) in
certain situations (ie, referral by dermatologist, ophthalmologist or gastroenterologist) and peripheral manifestations (arthritis, enthesitis, dactylitis) was also underlined.

In the subsequent discussion, several issues and concerns related to the use of a referral recommendation were raised. First, large differences across countries in the referral process and in the access of the referring physicians (ie, general practitioners, orthopaedic surgeons, dermatologists, gastroenterologist, ophthalmologist) to diagnostic methods (such as HLA-B27, imaging) have been pointed out. Second, some concerns regarding the interpretation of SpA features (eg, IBP, peripheral manifestations, laboratory and imaging parameters by non-rheumatologists) were raised. Finally, the well-known variation in prevalence of HLA-B27 among populations was mentioned as a possible concern.

As a result of the discussion, a first proposal for a referral recommendation was made. This proposal included the following key elements: (a) the entry criterion should be the presence of chronic back pain (duration ≥3 months) with an age of onset before 45 years; (b) this entry criterion could be combined with one or several referral parameters that in this stage were subdivided into two groups: ‘major’ parameters included IBP, HLA-B27 positivity and sacroiliitis on imaging; and ‘minor’ parameters included peripheral manifestations, extra-articular manifestations, positive family history for SpA and good response to NSAIDs; and (c) the final referral recommendation should allow adaptation to the needs of a local rheumatologist, specialists of the referring physician and local standards of care.

### The second Delphi round

A total of 106 full ASAS members were invited to participate in the second Delphi round, of which 86 (81%) responded. Ninety per cent of the ASAS members who completed the online survey agreed on the above-mentioned entry criterion (the presence of chronic back pain (duration ≥3 months) with an age of onset before 45 years). Furthermore, 64% of the experts were in favour of the combination of this entry criterion with at least one other referral parameter, while 28% of the responders did not consider the presence of other referral parameters obligatory for referral.

### Final discussion and final voting

At the ASAS annual meeting in 2014, a comprehensive summary of the previous rounds was provided and an update of the SLR was presented. Three papers reporting on referral strategies in SpA were additionally included and discussed. One study was already included as an abstract in the SLR, but now available in full text. In this study, a referral model based on a scoring system was proposed. The second study had reanalysed trial data and specifically investigated the contribution of HLA-B27 in a referral strategy. Based on their results, a two-step referral approach was proposed. The third study evaluated the agreement between primary care physicians and rheumatologist on referral parameters. Overall, the agreement was poor for IBP and sacroiliitis (kappa 0.16 and 0.31, respectively), moderate for a positive family history for SpA and HLA-B27 (kappa 0.50 and 0.59, respectively) and good for the presence of psoriasis, uveitis and inflammatory bowel disease (kappa 0.73, 0.81 and 0.87, respectively).

In the final voting, the majority of the participating ASAS experts (58%) were in favour of a combination of the entry criterion (chronic back pain with age of onset <45 years) with one or more additional referral parameter(s). There was an unanimous decision not to divide referral parameters into ‘minor’ and ‘major’ but to present the parameters as one list since only one parameter is required in addition to the entry criterion. Further concerns were expressed regarding imaging as a referral parameter, and the inclusion of elevated acute phase reactants (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) as an additional parameter was proposed. Finally, 78% of the voting members supported the combination of the entry criterion with any of the referral parameters. The inclusion of sacroiliitis on imaging (X-rays or MRI) as a referral parameter was supported by 52% of the experts, and a proposal to include

### Table 1  Summary of studies included in the systematic literature review

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Referring physician</th>
<th>Strategy</th>
<th>No. of patients referred</th>
<th>% axSpA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandt (2007)</td>
<td>Germany</td>
<td>GP</td>
<td>CLBP (&gt;3 months) and onset &lt;45 years plus ≥1 of: IBP, HLA-B27+, sacroiliitis IBP (Calin criteria, &gt;3 months) &lt;45 years</td>
<td>350</td>
<td>45.4</td>
</tr>
<tr>
<td>Hermann (2009)</td>
<td>Austria</td>
<td>GP and orthopaedic surgeon</td>
<td>IBP (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR))</td>
<td>92</td>
<td>32.6</td>
</tr>
<tr>
<td>Braun (2011)</td>
<td>Germany</td>
<td>Orthopaedic surgeon</td>
<td>CIBP (&gt;2 months and &lt;10 years) and onset &lt;45 years with inflammatory character as good response to NSAIDs according to computer algorithm</td>
<td>322</td>
<td>35.1</td>
</tr>
<tr>
<td>Poddubnyy (2011)</td>
<td>Germany</td>
<td>GP and orthopaedic surgeon</td>
<td>Strategy 1: CIBP (&gt;3 months) and onset &lt;45 years plus ≥1 of: IBP, HLA-B27+, sacroiliitis on imaging, good response on NSAIDs, positive family history of SpA Strategy 2: CIBP (&gt;3 months) and onset &lt;45 years plus ≥2 of: IBP, HLA-B27+, sacroiliitis on imaging, good response on NSAIDs, positive family history of SpA</td>
<td>Strat 1: 318 Strat 2: 242</td>
<td>41.8 36.8</td>
</tr>
<tr>
<td>Sieper (2013)</td>
<td>International</td>
<td>GP and other physicians</td>
<td>CIBP (&gt;3 months) and onset &lt;45 years plus ≥1 of: IBP, HLA-B27, sacroiliitis on imaging</td>
<td>Strat 1: 504 Strat 2: 568</td>
<td>35.6 39.8</td>
</tr>
<tr>
<td>Van den Berg (2013)</td>
<td>Netherlands</td>
<td>GP and other physicians</td>
<td>CIBP (&gt;3 months and &lt;2 years) and onset &lt;45 years</td>
<td>157</td>
<td>41.4</td>
</tr>
<tr>
<td>Brandt (EULAR 2012)</td>
<td>Germany</td>
<td>None (self-referral)</td>
<td>CIBP, online questionnaire using diagnostic algorithm</td>
<td>97</td>
<td>14.4</td>
</tr>
<tr>
<td>Weel (EULAR 2012)</td>
<td>Netherlands</td>
<td>GP</td>
<td>CIBP, identified from GP records</td>
<td>364</td>
<td>21.5</td>
</tr>
</tbody>
</table>

axSpA, axial spondyloarthritis; CIBP, chronic back pain; CLBP, chronic low back pain; EAM, extra-articular manifestation; EULAR, European League Against Rheumatism; GP, general practitioner; HLA, human leucocyte antigen; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis.
increased CRP or ESR in the list of the referral parameters was supported by 79% of the experts.

The final ASAS-endorsed recommendation for early referral of patients suspected for having axSpA by primary care physicians or non-rheumatologist is presented in box 1.

**DISCUSSION**

In this report, we present the first set of recommendations for referral of patients suspected of having axSpA by non-rheumatologists. The main intention of this initiative was to improve early diagnosis of axSpA around the world. Different referral strategies have been developed and tested in the past decade, mostly in Western Europe, and most recently also in the USA. All these strategies included one or several characteristic SpA features, and had a rather similar performance: by applying a referral strategy, the likelihood of axSpA in the referred populations increased from an assumed 5% to 30–40%. Although selection of the referral parameters in these strategies was primarily based on the expert opinion and in the majority of the studies no information on sensitivity and specificity of a certain approach was obtained, referral strategies were considered to be effective based on the proportion of patients diagnosed with axSpA by the rheumatologist. Therefore, the ASAS members decided to develop a consensual referral recommendation for patients suspected of having axSpA based on the available data.

The entry criterion of the ASAS-endorsed referral recommendation includes two features: the presence of chronic back pain, which is defined as back pain present for 3 months or longer, and back pain with an onset before the age of 45 years. This criterion is in agreement with the entry criterion of the ASAS classification criteria for axSpA. This definition of chronic back pain is widely used; however, currently data are lacking on whether applying a shorter or longer minimally required duration of back pain will change the final proportion of axSpA in the referred population. The vast majority of patients with axSpA experience the onset of back pain between 20 and 40 years of age, suggesting that a threshold of 45 years is a reasonable choice in order to capture >95% of patients with axSpA and in order to decrease the proportion of patients with primarily degenerative spinal problems among the referred patients. In addition, a threshold of 45 years provides face validity since a new onset of axSpA >45 years of age is broadly considered rare.

According to the consensual recommendation, the patient fulfilling the entry criterion should be referred to a rheumatologist if at least one of the referral parameters is positive (box 1). The list of the parameters includes the most relevant SpA features selected by consensus and based on the currently available evidence. Many referral strategies tested in the past have included IBP as a mandatory referral parameter. Although in practice IBP is frequently used as a referral parameter, studies have shown that patients referred with IBP being present do not have a higher likelihood of being diagnosed with axSpA than patients referred without inflammatory characteristics. Furthermore, IBP as a concept and practical screening tool is difficult to perform in practice because of operator characteristics leading to the poor agreement among referring physicians and rheumatologists regarding the presence of this feature. However, since IBP was considered a hallmark of SpA by most experts, ASAS members still felt the need to include this parameter in the final set of parameters, but not as an entry criterion. This is also in line with the updated algorithm for diagnosing axial SpA, which does not have IBP as a mandatory criterion but only as one of the possible SpA features.

The proposed recommendation represents a universal and flexible approach, which could be adapted to local regulations, standards of clinical practice and type of referring physicians. For instance, if referring physicians do not perform imaging of the sacroiliac joints, or order HLA-B27, these items of the referral parameter list could be ignored. Such an approach could be offered to nearly every non-rheumatologist (orthopaedic surgeon, gastroenterologist, ophthalmologist, dermatologist),...
who may see patients with possible axSpA. For example, a simple referral strategy for a gastroenterologist would include the referral of all patients with inflammatory bowel disease that report chronic back pain with an age of onset before 45 years. In analogy, for the ophthalmologist the strategy would be to refer all patients with (a history of) acute anterior uveitis that report chronic back pain with an age of onset before 45 years. For these medical specialists, the referral strategy only implies a few brief questions asked to the patient.

We hope that the recommended consensual referral strategy, which is based on the opinion of the expert society taking currently available evidence into account, is an important step towards early diagnosis of axSpA. The performance of the strategy in different countries with participation of different non-rheumatologic referring specialists should be tested in further studies.

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Contributors All authors contributed to acquisition, analysis and interpretation of the data and drafting the manuscript.

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