A national survey on the management of psoriatic arthritis using the Delphi method

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Abstract

Objective

Accurate diagnosis and appropriate management of psoriatic arthritis (PsA) is essential to avoid unnecessary morbidity. Our aim in this study was to evaluate the current approach to the management of PsA among rheumatologists.

Methods

A 16-item online questionnaire, produced using the Delphi method, was submitted to a panel of rheumatologists who anonymously expressed their opinions on a scale from 1 (maximum disagreement) to 5 (maximum agreement). Positive consensus was defined by ≥66% of the respondents scoring an item 3, 4 or 5. Negative consensus was defined by ≥66% of the respondents scoring an item 1 or 2.

Results

The surveyed rheumatologists agreed that in its early stage, PsA is characterised by the involvement of few joints and/or entheses and that psoriasis, although possibly absent, will be present in a patient's past personal or family history. There was no consensus among the rheumatologists regarding normalisation of C-reactive protein levels and erythrocyte sedimentation rates defining remission. The specialists believed that clinical remission was achieved more frequently and for longer among patients with PsA than rheumatoid arthritis. The participants believed that neutralising antibodies altered the efficacy of anti-tumour necrosis factor agents and that monoclonal antibodies induced greater production of neutralising antibodies than receptor proteins. However, knowledge was somewhat lacking in relation to the prophylaxis of latent tuberculosis.

Conclusion

The data collected showed that the surveyed rheumatologists had a good knowledge of the diagnosis of early-stage PsA and a good understanding of its management in relation to its clinical phenotype, with the exception of the form having predominantly axial involvement.

Key words

Delphi method, psoriatic arthritis, spondyloarthritis, survey, disease management

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What is already known about this topic?

Psoriatic arthritis (PsA) is associated with substantial morbidity, and a widely varying and unpredictable clinical course. Timely diagnosis, referral to a rheumatologist and prompt treatment are key to maximising outcomes.

What does this study add?

The large panel of rheumatologists surveyed had a good knowledge of early-stage PsA diagnostic criteria, but less understanding of clinical remission.
There was general awareness of the appropriate use of anti-tumour necrosis factor therapy. However, knowledge was somewhat lacking in relation to latent tuberculosis prophylaxis.

Introduction

Psoriatic arthritis (PsA) is a chronic condition characterised by inflammation of synovial tissue, entheses and skin, while patients are usually seronegative for rheumatoid factor (1). PsA is currently classified in the spondyloarthritis group (2, 3).
The clinical presentation of PsA is heterogeneous with diverse articular and dermatological features, and varied disease courses and outcomes. While initially considered to be a mild disease, PsA has since been found to develop into an erosive and deforming form in 40-60% of patients (4). Furthermore patients with PsA have a reduced quality of life, functional impairment, psychosocial disability and a greater risk for death than the general population (5). The radiological features of PsA consist of destructive changes and new bone formation (6).
Recent studies have shown that remission of PsA symptoms is attributed to early diagnosis and treatment (7,8). However, the prevalence of psoriasis is 2-3% while PsA occurs in about one-third of patients with psoriasis (9), indicating that many individuals with PsA are undiagnosed (10,11), possibly due to under-recognition of PsA symptoms or a lack of effective screening tools (12). The management of PsA has changed enormously over the past decade owing to early diagnosis and improvement in treatment strategies, including early referral by dermatologists and primary care physicians to rheumatologists, prompt initiation of therapy and advances in pharmacological therapy (10). Traditional therapies for PsA include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs) (13). However, conventional synthetic DMARDs are ineffective or unsatisfactory in certain types of pain, peripheral symptoms and in stopping the progression of bone damage, leading to difficulty in the definition of clinical remission (14). Consequently, anti-tumour necrosis factor (anti-TNF) agents represent a revolution in the treatment of PsA. They reduce the signs and symptoms of inflammation, improve function and quality of life, delay the progression of peripheral joint damage and manage skin manifestations (13, 15). Anti-TNF agents are usually prescribed only after the failure of NSAIDs, steroids and traditional DMARDs (10).
It is widely recognised that there are gaps and unmet needs in the diagnosis and treatment of PsA that underlie the poor clinical and functional outcomes in patients with PsA. Unmet needs that should be addressed across all aspects of the assessment and management of PsA includes diagnosis of PsA, physician and patient awareness of the disease, identification of at-risk and high risk patients, lack of validated treatment algorithms and/or consensus on treatment success, lack of awareness of the burden of PsA on patient lives, awareness of the impact of comorbidities, and value and cost-effectiveness of PsA therapies (16, 17).
Therefore, the aim of the present study was to carry out a national survey on PsA diagnosis and management by using the Delphi method in a setting of rheumatologists, to evaluate the level of knowledge among practicing rheumatologists.

Methods

Participants

A total of 266 rheumatologists were recruited to participate to the study. In particular, the survey was endorsed by the Italian Society for Rheumatology and the statements were sent to rheuma-

tologists members of this society, geographically distributed throughout the country and representative of physicians involved in treating patients with inflammatory arthritis. To avoid selection bias, the rheumatologists were chosen randomly and additional information about them was specifically not requested. An information letter giving the details of the survey procedure was then sent to all of the rheumatologists and those willing to participate were invited to anonymously complete a questionnaire.

Questionnaire

Using the Delphi method, an on-line questionnaire consisting of 16 items was prepared and submitted to the panel of rheumatologists, who expressed their opinions anonymously. The 16 items were designed to define opinions in a range of topics, including the nature of presenting and early-stage PsA symptoms, remission criteria, latent tuberculosis, the treatment of PsA and patient-related outcomes. All co-authors joined the meeting in which was defined the main domains to be evaluated by the Delphi method, and each of them prepared some statements on the domains. Then, during a second meeting, the final 16 items were chosen by all co-authors and deemed suitable for the questionnaire.

The Delphi questionnaire offered two grades of disagreement (1 'strongly disagree', 2 'disagree') and three grades of agreement (3 'slightly agree', 4 'agree', 5 'strongly agree'. A consensus was considered positive when ≥66% of the participants gave a score of 3, 4 or 5, while a consensus was considered negative when ≥66% of the participants gave a score of 1 or 2.

Results

Clinical profile of early-stage PsA

• *Joint involvement in early-stage PsA*

The rheumatologists surveyed overwhelmingly agreed that early-stage PsA was most frequently an oligoarthritic (89%) or oligo-enthesoarthritic (93%) condition, while 67% of those interviewed did not agree that early-stage PsA manifested as a spondylitis. A consensus was not reached on whether early-stage PsA was considered a rheumatoid-like condition (Fig. 1).

	Delphi survey response 1	2	3	4	5
Early-stage PsA is most commonly:					
A spondylitic condition	67%			33%	
A rheumatoid-like condition	65%			35%	
An oligoarthritic condition	11%			89%	
An oligo-enthesoarthritic condition	7%			93%	
In early-stage PsA, psoriatic manifestations of the skin and/or nails:					
Must always be present	86%			14%	
May be absent	29%			71%	
May be absent, but there must be a past personal or family history	14%			86%	
Must be present, but only concerning the skin; nail involvement is not specific	88%			12%	
The earliest evidence of oligo-enthesoarthritis can be obtained by using:					
Traditional radiology	83%			17%	
Ultrasonography	5%			95%	
Magnetic resonance imaging	8%			92%	
Ultrasonography and/or magnetic resonance imaging	6%			94%	
Careful clinical examination	19%			81%	

Survey responses were: 1, strongly disagree; 2, disagree; 3, slightly agree; 4, agree; 5, strongly agree.

= Negative consensus; = No consensus; = Positive consensus

Fig. 1. Beliefs surrounding the presentation, cutaneous manifestations and clinical pattern of early-stage psoriatic arthritis.

	Delphi survey response 1	2	3	4	5
There is no scientific evidence for a lack of association between clinical remission and progression of radiologically detectable damage	37%			63%	
After 1 year of treatment with DMARDs (including biological agents), about 1/3 of patients with PsA achieve remission	27%			73%	
The frequency of patients in remission is higher among patients with PsA than RA	27%			73%	
After stopping treatment with DMARDs, remission lasts longer in patients with PsA than RA	31%			69%	

Survey responses were: 1, strongly disagree; 2, disagree; 3, slightly agree; 4, agree; 5, strongly agree.

= Negative consensus; = No consensus; = Positive consensus

DMARDs, disease-modifying antirheumatic drugs; PsA, psoriatic arthritis; RA, rheumatoid arthritis

Fig. 2. Beliefs surrounding the frequency and duration of clinical remission in psoriatic arthritis.

• *Role of the presence of psoriasis in early-stage PsA*

The rheumatologists surveyed disagreed that psoriasis of the skin and/or nails must always be present in early-stage PsA (86%) and, likewise, disagreed that cutaneous manifestations of psoriasis must be present in early-stage PsA (88%). In contrast, there was positive consensus on whether psoriatic manifestations could be absent (71%), but that the patient must have a past personal or family history of such manifestations (86%) (Fig. 1).

• *Role of imaging for oligo-enthesoarthritis in early-stage PsA*

The participants concordantly disagreed (83%) that the first evidence of oligo-enthesoarthritis in early-stage PsA could be obtained using traditional radiology. Conversely, they concordantly agreed that ultrasonography (95%), magnetic resonance imaging (MRI, 92%), either or both of these imaging techniques (94%), or a careful clinical examination (81%) could promptly demonstrate oligo-enthesoarthritic involvement in early-stage PsA (Fig. 1).

Clinical remission of PsA

• *Criteria for defining clinical remission of PsA*

The rheumatologists agreed that PsA was in remission when there was absence of joint swelling and/or tenderness (81%) or absence of inflammatory-type back pain, enthesitis, dactylitis or extra-articular manifestations of the PsA (94%). However, a consensus was

not reached on whether remission was achieved if a patient had normal values for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), or a Disease Activity Score in 28 joints (DAS28) of <2.6 (Supplementary Fig. 1).

• *Frequency and duration of clinical remission in patients with PsA*
The majority (73%) of the rheumatologists surveyed stated that after 1 year of treatment with DMARDs, including biological agents, about one-third of patients with PsA achieved clinical remission and that the latter proportion was higher than for RA. The survey participants agreed that after stopping treatment with DMARDs, remission lasted longer in patients with PsA than RA (Fig. 2).

Tuberculosis and treatment of PsA
• *Screening for latent tuberculosis*
There was agreement that, besides chest x-rays, screening for latent tuberculosis should include the Mantoux reaction (76%), the Quantiferon test (71%), or both (70%) (Fig. 3).

• *Prophylaxis of latent tuberculosis*
The surveyed rheumatologists agreed on the use of isoniazid for the prophylaxis of latent tuberculosis (85%), while there was a negative consensus on the use of ethambutol (83%) and the combination of isoniazid/rifampicin/ethambutol (87%). A consensus was not reached on the use of rifampicin alone or in combination with isoniazid in the prophylaxis of latent tuberculosis (Fig. 3).

• *Duration of latent tuberculosis prophylaxis*
Seventy-one percent of the rheumatologists surveyed believed that prophylaxis of latent tuberculosis with isoniazid should be continued for 9 months. They did not consider 6 months of prophylaxis with soluble TNF receptor (78%) or 9 months of anti-TNF monoclonal antibody prophylaxis (69%) to be appropriate (Fig. 3).

Therapy in relation to clinical phenotype of PsA
• *The clinical form of PsA and its impact on therapeutic approach*
There was extensive agreement that the clinical form of PsA impacted on therapy with each form requiring a different approach. No consensus was reached on whether peripheral or axial involvement, or only the intensity of the arthritis, influenced the therapeutic approach (Supplementary Fig. 2).

	Delphi survey response	
	1 2 3	4 5
Besides chest X-rays, tuberculosis screening should involve:		
The Mantoux reaction	24%	76%
The Mantoux reaction + Quantiferon test	30%	70%
The Quantiferon test	29%	71%
Either the Quantiferon test or the Mantoux reaction	62%	38%
Appropriate prophylaxis of latent tuberculosis is:		
Isoniazid	15%	85%
Ethambutol	83%	17%
Rifampicin	65%	35%
Isoniazid+ rifampicin	63%	37%
Isoniazid + rifampicin + ethambutol	87%	13%
Prophylaxis with isoniazid should be continued for:		
6 months	59%	41%
9 months	29%	71%
6 months only if combined with a soluble TNF receptor	78%	22%
9 months if combined with a monoclonal anti-TNF	69%	31%

Survey responses were: 1, strongly disagree; 2, disagree; 3, slightly agree; 4, agree; 5, strongly agree.
= Negative consensus; = No consensus; = Positive consensus
TNF, tumour necrosis factor

Fig. 3. Beliefs surrounding the screening, and choice and duration of prophylaxis for latent tuberculosis.

	Delphi survey response	
	1 2 3	4 5
Compared with receptor proteins, monoclonal antibodies induce greater production of neutralising antibodies	13%	87%
Monoclonal antibodies and receptor proteins can induce the production of neutralising antibodies	19%	81%
Receptor proteins have less potential to induce production of neutralising antibodies than monoclonal antibodies	19%	81%
The amount of neutralising antibodies produced does not depend on the molecular structure of biological agent	75%	25%

Survey responses were: 1, strongly disagree; 2, disagree; 3, slightly agree; 4, agree; 5, strongly agree.
= Negative consensus; = No consensus; = Positive consensus

Fig. 4. Beliefs surrounding differences in immunogenicity between monoclonal antibodies and receptor proteins.

• *Use of anti-TNF agents in predominantly axial PsA*
The rheumatologists surveyed did not reach a consensus on any of the statements concerning the use of anti-TNF agents in predominantly axial PsA (Supplementary Fig. 2).

• *Use of anti-TNF agents in predominantly peripheral PsA*
The rheumatologists agreed (92% concordance) that the use of anti-TNF agents in predominantly peripheral PsA should be considered when there was persistent inflammation despite treatment with NSAIDs, traditional DMARDs and steroid injections. Almost as many (86%) also agreed with the use of anti-TNF agents in the presence of new erosions or worsening of previously present erosions, even when there was a satisfactory response to non-biological DMARDs. Most (67%) of the participants did not believe that anti-TNF agents should be used with non-biological DMARDs to reduce side effects (Supplementary Fig. 2).

• *Use of anti-TNF agents in PsA with enthesitis and/or dactylitis*
The rheumatologists agreed that the use of anti-TNF agents in PsA characterised

by enthesitis and/or dactylitis should be considered in the presence of active enthesitis or dactylitis, a lack of response to NSAIDs and one traditional DMARD for at least 3 months and to at least two local injections of steroids (79%). Almost the same proportion of rheumatologists (76%) considered that anti-TNF agents should be used in the presence of active enthesitis or dactylitis and a lack of response to NSAIDs and local steroid injections. Most (69%) did not believe that this treatment was appropriate for enthesitis or dactylitis diagnosed using clinical criteria or on the basis of expert opinion (Supplementary Fig. 2).

Immunogenicity and anti-TNF therapy in PsA

• *Role of immunogenicity in the efficacy of treatment*

The rheumatologists surveyed agreed that neutralising antibodies could modify the efficacy of PsA treatment (90%). However, a consensus was not reached on whether non-neutralising antibodies could alter the efficacy of treatment, whether immunogenicity was related only to the presence of neutralising antibodies or whether immunogenicity depended on the presence of both neutralising and non-neutralising antibodies (Supplementary Fig. 3).

• *Differences in immunogenicity between monoclonal antibodies and receptor proteins*

There was agreement among the surveyed rheumatologists that monoclonal antibodies and receptor proteins could induce the formation of neutralising antibodies (81%), that monoclonal antibodies induced greater production of neutralising antibodies than protein receptors (87%) and that the latter usually induced the production of fewer neutralising antibodies (81%). Most (75%) of those surveyed disagreed with the statement that the amount of neutralising antibodies produced did not depend on the molecular structure of the biological agent (Fig. 4).

Patient-reported outcomes in PsA

• *Use of patient-reported outcomes in clinical practice*

The rheumatologists agreed that patient-reported outcomes (PRO) should be recorded in the outpatient clinic at regular intervals (94%) and that they should be used to create regional and/or national registries to determine the efficacy of treatment with biological agents (90%) (Supplementary Fig. 4).

• *Patient-related outcome domains*

The participants surveyed agreed that PRO regarding overall evaluation of the disease (90%), quality of life (92%), pain (93%) and physical disability (92%) played an important role in the clinical management of patients with PsA (Supplementary Fig. 4).

Discussion

Our Delphi survey provided an insight on how some aspects of PsA management are approached. It was obtained by opinions among a panel of rheumatologists working in clinical practice in throughout Italy. To our knowledge, this represents the largest panel of rheumatologists enrolled in such a survey designed to explore the management of patients with PsA. A recent Spanish survey also used the Delphi approach to formulate rheumatologist- and dermatologist-based recommendations for PsA management (18). The Delphi approach has also been used to help dermatologists recognise the symptoms of PsA and collaborate with rheumatologists to improve the detection and management of the condition (19, 20).

The rheumatologists surveyed in our study were in general agreement over the clinical presentation of early-stage PsA, which largely mirrors published data supporting the notion that the clinical spectrum of PsA is heterogeneous and that the condition affects both peripheral joints and the axial skeleton (1, 21-31).

A diagnosis of PsA can be made according to the presence of a proportion of several possible features characteristic of the condition, such as current psoriasis, or personal of family history of psoriasis (10, 32-36). Consistent with this, our surveyed rheumatologists agreed that skin or nail manifestations may in fact be absent in early-stage PsA, although there may be a past personal or family history of such manifestations.

Moreover, consistent with published literature, the majority of the rheumatologists surveyed believed that careful clinical examination and ultrasonography, MRI, either or both of these in combination, were the most useful investigations for the prompt detection of oligo-enthesoarthritic involvement in early-stage PsA. They considered traditional radiology to be unsuitable for this purpose. Another topic of the present survey was the issue of remission in PsA patients. Most of the rheumatologists agreed that patients may be in clinical remission in the absence of joint swelling and/or tenderness, inflammatory-type back pain, enthesitis, dactylitis and extra-articular manifestations. These opinions are partially in agreement with the literature. While there is no commonly accepted definition of remission in PsA (14), criteria have been proposed that consider symptoms such as fatigue, pain, articular morning stiffness, and ESR and CRP values (37) or by using validated instruments such as the Disease Activity index for Psoriatic Arthritis (DAPSA) (38). Of note, there was a lack of consensus among the surveyed rheumatologists on whether scientific evidence was available demonstrating a lack of association between clinical remission and progression of radiologically detectable damage. Indeed, this topic is still a challenge for the rheumatologist, namely trying to demonstrate that clinical remission is always associated with a "deep remission" detected by imaging. Therefore, the definition of complete, sustained remission should not be based on clinical assessments alone, but should also include confirmation of the absence of subclinical inflammation using sensitive imaging techniques such as ultrasonography and MRI.

In our survey, the rheumatologists believed that clinical remission was more common and lasted longer among patients with PsA than RA. The published evidence for this is contradictory, with some reports of similar rates of remission for both conditions, while others show a higher rate and a longer duration of remission for PsA (37, 39-43).

A recent survey showed how rheumatologists are highly aware of anti-TNF-related risk of tuberculosis with variable

LTBI screening and tuberculosis prevention strategies (44). Indeed, most of the surveyed rheumatologists agreed that screening for latent tuberculosis should be done using the Mantoux reaction, the Quantiferon test or both, in addition to chest radiology. Guidelines recommend specific screening and prophylaxis for latent tuberculosis before beginning anti-TNF therapy (45-47). Most of the surveyed participants agreed on the suitability of isoniazid and the unsuitability of ethambutol or the combination of isoniazid/rifampicin/ethambutol for latent tuberculosis prophylaxis. The most effective and least toxic first-line agents are isoniazid, rifampicin and ethambutol (48, 49). As indicated by the majority of respondents, daily isoniazid for 9 months is the standard prophylactic regimen for latent tuberculosis (50). In contrast to published data, surveyed rheumatologists disagreed that the duration of isoniazid prophylaxis should be 6 months if combined with soluble anti-TNF agents and 9 months if combined with monoclonal anti-TNF antibodies. In these cases, the specialists' opinions are not consistent with the literature. A 6-month course of isoniazid chemoprophylaxis is efficacious in combination with the soluble anti-TNF agent, etanercept (51). The survey dealt with an important potential effect of treatment with anti-TNF agents, namely the development of immunogenicity. Immunogenicity refers to the ability of biological therapies to instigate an immune response, thereby leading to a loss of efficacy (52). We questioned the panel of rheumatologists on their knowledge of differences in immunogenicity between monoclonal antibodies and receptor proteins. Most of the respondents agreed that both types of biological agents could induce neutralising antibodies and that monoclonal antibodies induced a greater production of neutralising antibodies than receptor proteins. They concordantly disagreed that the amount of neutralising antibodies produced was independent of the molecular structure of the biological agent. This is broadly in agreement with the literature. Immunogenicity is the most likely reason for loss of anti-TNF agent efficacy and the agents have different potential for immunogenicity mainly because of differences in their molecular structure (53-55). However most of these aspects are in keeping with a number of general principles of the management of PsA patients treated with anti-TNF agents and, to certain extent, with those reported in the literature (56-58).

The rheumatologists in our survey agreed that PRO should be recorded regularly during outpatient visits and used in regional/national registries, reflecting the view in published literature that this information is important to guide management, improve patient-clinician communication, enhance outcomes and provide additional information on safety and comparative efficacy in PsA patients (59-62).

There are potential limitations of our study. First of all, selection of doctors involved in the survey was randomly chosen and based on their expertise. This is a possible weakness but, to a certain extent, a strength since all doctors who participated in the Delphi showed their knowledge on important practical aspects of clinical management. Indeed, the results obtained are in keeping with data from the literature and showing a possible fully understanding of the statements proposed and discussed, in a large sample of rheumatologists. Secondly, as a potential bias in the methodology, there were only two options in the questionnaire for participants to disagree ('strongly disagree' and 'disagree') with the statements, whereas there were three options for agreement ('slightly agree', 'agree' and 'strongly disagree') with statements. This may have positively biased the responses for agreeing with the statements.

In conclusion, we found that the surveyed rheumatologists had good knowledge of the diagnostic criteria for early-stage PsA, but had less understanding of clinical remission in PsA. Participants were confident in their use of anti-TNF agents according to PsA phenotype, with the exception of PsA having predominantly axial involvement. Knowledge was somewhat lacking in relation to the prophylaxis of latent tuberculosis. We ascertained from our survey that the participants were aware of the importance of PRO in standard rheumatology practice and in the clinical management of patients with PsA.

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