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Management of Psoriatic Arthritis in Patients With Comorbidities: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations

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ABSTRACT. ***Objective.*** The 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations provide an evidence-based guide for selecting therapy based on the individual's disease features. Beyond the disease features and associated conditions (eg, uveitis and inflammatory bowel disease), comorbidities play an important role in selecting therapy for an individual patient.

Methods. We performed a systematic literature review. We examined the available evidence to inform treatment selection based on the presence or absence of comorbidities in psoriatic arthritis (PsA).

Results. Common comorbidities in PsA that may affect treatment selection include presence of baseline cardiovascular disease (CVD) or high risk for CVD, obesity and metabolic syndrome, liver disease, mood disorders, including depression in particular, chronic infections, malignancies, osteoporosis, and fibromyalgia and/or central sensitization.

Conclusion. Comorbidities may influence both the effectiveness of a given therapy but also the potential for adverse events. It is important to assess for the presence of comorbidities prior to therapy selection.

Key Indexing terms: comorbidities, GRAPPA, psoriatic arthritis, treatments

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Psoriasis (PsO) and psoriatic arthritis (PsA) are associated with several chronic conditions that may negatively affect treatment response, treatment-related adverse events (AEs), quality of life, and longevity. Comorbidities of importance in PsA include cardiovascular disease (CVD), obesity and metabolic syndrome, liver disease (nonalcoholic fatty liver disease [NAFLD]), mood disorders including depression/anxiety, chronic infections, malignancies, osteoporosis, and fibromyalgia (FM) and/or central sensitization. The above must be considered during the holistic evaluation of patients with PsA prior to selection of therapy and monitoring. Further, identifying comorbidities through screening may improve patient outcomes and longevity. In a Danish cohort of patients with PsA, comorbidities were associated with higher baseline disease activity, shorter tumor necrosis factor inhibitor (TNFi) survival, and reduced clinical response to therapy.[1] PsA is also associated with extraarticular manifestations, which include uveitis and inflammatory bowel disease. These associated conditions are discussed by another working group. The objectives of our group were to (1) understand how comorbidities affect treatment choices and guide drug selection, and (2) make evidence-based recommendations regarding screening for comorbidities in patients with PsA. In this paper, we address select comorbidities that influence treatment selection, the potential for adverse events, and those that affect quality and length of life. These data were analyzed to inform treatment selection in the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations.

METHODS

Study design. We used PICO (Patient/Population – Intervention – Comparison/Comparator – Outcome) and performed an evidence review to address the following question: among patients with PsA (P), does having comorbidity x (I), compared to not having comorbidity x (C), impact treatment outcomes, including benefits and harms (O)? Two systematic literature reviews were performed.

Eligibility criteria. Included studies addressed adults with PsA. If the patient population in the study was mixed, over half had to be adults and over half had to have PsA. Studies also needed to address ≥ 1 of the following comorbidities: CVD, obesity, metabolic syndrome, fatty liver disease, mood disorder (anxiety/depression), chronic infections (hepatitis B [HBV], hepatitis C [HCV], HIV, tuberculosis [TB]/latent TB, fungal infection, herpes zoster), malignancy, osteoporosis, and/or FM. Studies included were comparative studies (nonrandomized), before-and-after studies, and cohort studies. Qualitative studies, case series and case studies, secondary evidence from reviews or recommendations, conference abstracts, editorials, commentaries, trial protocols, and letters were excluded.

Among these studies, 2 types of questions were addressed. For studies examining the effect of a given comorbidity compared to not having the comorbidity on treatment response or AEs, the study needed to include a pharmaceutical intervention. Nondrug, surgical, complementary/alternative medicine, and service level interventions were not addressed in this review. Additionally, these studies were required to have a response outcome (eg, ACR20/50/70, imaging outcome, patient-reported outcomes [PROs], or disease progression measures) or AE outcome (side effects and/or AEs). For studies addressing screening, we examined studies addressing prevalence, outcomes, or screening methods for the named comorbidities in patients with PsA.

Literature search. Two literature search updates were performed starting February 19, 2013.[2] The search strategies are provided in the Supplementary File (available with the online version of this article). The first addressed the impact of comorbidities on treatment outcomes and was run on March 30, 2020. The second addressed screening for comorbidities and was run on January 13, 2021.

Data extraction. After completing the initial search, 2 reviewers independently assessed inclusion/exclusion criteria. Members of the working group then reviewed individual papers for full-text review and abstracted key data on PICO (Table 1). We divided the search results into the relevant topics and working group members extracted data from each of the relevant papers and also performed hand searches to extract additional information from related papers.

Synthesis of results. We qualitatively summarized results from the review. From this data, we created a set of statements about each topic area. We then performed a Delphi process within our working group. Members of the working group were asked to vote on agreement or disagreement with each statement. Areas of disagreement were refined and a repeat vote on those items was conducted. With regard to screening recommendations, we specifically did not denote who should perform the screening as this may have varied by country and/or region.

Ethics. This paper does not require institutional review board (IRB)/animal approval.

RESULTS

Impact of comorbidities on treatment outcomes. The search identified 2170 unique articles, of which 143 papers were selected for full-text review. A total of 40 papers met the review criteria. Among these, 21 were prospective cohort studies, 11 were retrospective cohort studies, 2 were case-control studies, 4 were before-and-after studies, and 2 were cross-sectional studies. The types of comorbidities covered are shown in Table 2. Below we summarize the available evidence for each of the selected comorbidities. In Table 3, we summarize the recommendations made by this panel and the voting among the 20 voters.

CVD. A number of studies have demonstrated increased incidence and prevalence of CVD in patients with PsA compared to patients without PsA.[3] Additionally, several studies have suggested that the greater the disease activity, the greater cardiovascular (CV) risk, independent of disease duration and other demographic factors.[4] Disease Activity in Psoriatic Arthritis (DAPSA) score increases were associated with a higher number of CV risk factors.[4] In patients with established CVD (coronary artery disease, previous strokes, and/or myocardial infarctions), nonsteroidal antiinflammatory drugs (NSAIDs) pose a challenge.[5] All NSAIDs confer the same risk of CV events, which should be considered when prescribing these drugs.[5]

There is a relative dearth of observational studies to inform the association of treatment and risk of CVD in patients with PsA. However, TNFi and methotrexate (MTX) may improve arterial stiffness, intima-media thickness, and endothelial dysfunction.[6] TNFi may reduce the risk for myocardial infarction (MI) in patients with PsA.[7] However, without randomized controlled trials, there is not yet sufficient evidence to suggest that treatment of PsA improves long-term CV risk. For this reason, the focus remains on identifying and managing individual CV risk factors.

Obesity and metabolic syndrome. Patients with PsO and those with PsA have an increased prevalence of obesity as well as metabolic

Table 1. PICO questions addressed in patients with psoriatic arthritis (PsA).

Patient	Intervention	Comparison	Outcomes
PsA	CVD Obesity and metabolic syndrome Fatty liver disease Mood disorders Chronic infections Malignancy Osteoporosis Chronic pain/fibromyalgia	Patients without these comorbidities	Influences treatment choice (eg, response to therapy or adverse events) Comorbidities may be worsened by therapy

CVD: cardiovascular disease; PICO: Patient/Population – Intervention – Comparison/Comparator – Outcome; PsA: psoriatic arthritis.

Table 2. Types of comorbidities addressed by full-text manuscripts meeting inclusion criteria.

Comorbidities	No. of Studies
Concomitant CVD	9
Obesity + metabolic syndrome	10
Liver disease (eg, fatty liver/NASH)	2
Mood disorders (depression/anxiety)	5
Chronic infections (HBV, HCV, HIV, TB/LTBI, fungal, herpes zoster)	4
Malignancy (skin cancer, lymphoma, other)	0
Osteoporosis	1
Chronic pain/fibromyalgia	1
Drug survival predictors	8
Total no. of studies	40

CVD: cardiovascular disease; HBV: hepatitis B virus; HCV: hepatitis C virus; LTBI: latent tuberculosis infection; NASH: nonalcoholic steatohepatitis; TB: tuberculosis.

syndrome.[8-15] Not only do these comorbidities increase the risk for the development of PsO and PsA, but obese patients may have a poor response to therapy compared to nonobese patients and have more disease activity, including higher Psoriasis Area and Severity Index (PASI) scores.[15] Weight loss in obese patients is associated with improved response to therapy.[15-17] Patients with PsA have an increased risk for metabolic syndrome with low levels of high-density lipoprotein, triglyceride, and total cholesterol.[11] Metabolic syndrome is also often associated with more severe PsA.[12,18]

Liver disease. PsO and PsA are associated with nonalcoholic steatohepatitis (NASH), which is closely related to the presence of metabolic syndrome. Many of the drugs used to treat PsO and PsA are themselves associated with hepatotoxicity, and the presence of chronic liver disease can make therapy selection more difficult. Treatment with NSAIDs, MTX, leflunomide (LEF), and occasionally TNFi and Janus kinase inhibitors (JAKi) may result in hepatotoxicity and abnormalities in liver function tests.[19,20] However, in 1 study, patients with PsA treated with a combination of anti-TNF and MTX had a lower risk of hepatic fibrosis than patients treated with MTX alone.[21] MTX and LEF are known to cause liver function abnormalities as well as the development of NASH or NAFLD.[22] Liver disease may result from the disease itself since patients with rheumatoid arthritis (RA) on the same medication do not have a similar prevalence of liver disease.[23-26]

Chronic HBV and HCV infection. There is limited published literature on the incidence and prevalence of HBV and HCV in patients with PsA. Costa et al evaluated 15 patients with PsA who were positive for HCV and treated with anti-TNF therapy. All achieved minimal disease activity with low viral load and liver enzymes remained stable at 12 months.[27] Minimal data exist to examine the safety of other biologics in the setting of viral hepatitis. When making treatment decisions for these patients, working with a hepatologist/gastroenterologist is important. These patients may require concomitant treatment with an approved antiviral medication directed against HBV. International recommendations dictate the screening for HBV and hepatitis HCV prior to commencing MTX and biologic disease-modifying antirheumatic drugs (bDMARDs), which require periodic testing depending on individual patient risks and in areas where these infections are endemic.[28,29]

Mycobacterium tuberculosis *infection.* There is limited data on the prevalence of TB in patients with PsA. However, it is well known that the incidence of active TB increases in patients receiving TNF inhibitor therapy. The presence of concomitant latent TB infection in patients with PsA did not influence the effectiveness of anti-TNF therapy during the follow-up period.[30]

Candida *infection.* Patients with PsA on IL-17 inhibitors have a greater risk for the development of *Candida* infection. Usually, these infections are mild to moderate in severity and resolve with antifungal therapy. Asking patients about *Candida* infections and maintaining a high index of suspicion is recommended in patients using these therapies. Asking about *Candida* infections may be appropriate before starting an IL-17 inhibitor.[31-33]

Herpes zoster infection. In some studies, patients with PsO and PsA have higher rates of herpes zoster (HZ) compared to the general population. Patients taking TNFi may present with more severe HZ and the JAKi tofacitinib confers a 2 to 3-fold higher risk than patients on anti-TNF therapy for the development of HZ.[34] Effective inactivated vaccines against HZ are now available and should be considered in this patient population.

Depression. Depression is a major health concern in patients with PsO and PsA. Patients with PsO who have major depression are

Table 3. Summary recommendations relating to comorbidities in patients with PsA.

Identification of Comorbidities	Agreement, %
CV risk is elevated in patients with PsA. Patients should be screened for CV risk factors and these risk factors should be managed to improve CV outcomes in this patient population. Screening for CV risk and risk factors may be accomplished by any of the healthcare providers caring for the patient (ie, rheumatologist, dermatologist, cardiologist, PCP).	100
Several studies have demonstrated that obesity is associated with reduced functional ability, greater psoriasis severity and disease activity, and reduced response to therapy. Patients should be encouraged to maintain a healthy weight in order to improve disease activity and disease impact.	100
Fatty liver disease is common in patients with PsA, often related to obesity and/or diabetes. This should be considered when monitoring LFTs on medication and when selecting therapies that may affect the liver.	100
Immunomodulatory therapies used in PsA can affect untreated HBV, HCV, or HIV. Patients should be screened for active HBV and HCV prior to therapy initiation. Seek gastroenterology/hepatology input regarding the use of antivirals when initiating patients with active HCV or active or past HBV on therapy. Patients should likewise be screened for HIV and treatment decisions should be made in collaboration with an infectious disease specialist.	100
TB is a serious infection and is common in some parts of the world. Biologic therapies, particularly TNFi, can increase the risk of developing active TB. Screening for active or LTBI is recommended prior to initiation of therapy.	100
Herpes zoster can be a complication of immunomodulatory therapies although this risk appears to be higher with JAKi. Rheumatologists should counsel patients about this risk and encourage vaccination prior to starting therapy when accessible.	100
Some of the immunomodulatory therapies and prior phototherapy are associated with an increased risk for nonmelanoma skin cancer. Patients should be counseled about this risk and should be encouraged to undergo full skin assessment annually.	90
Osteoporosis surveillance and treatment should be the same in patients with PsA compared to the general population.	100
FM and/or CS is associated with poor QOL and diminished response to therapy. Identification and management of FM/CS may improve the patient's overall QOL and diminish treatment cycling.	100
Depression and anxiety have a high prevalence in PsA and are strong negative predictors of joint remission in patients with PsA. Screening for mood disorders should be part of the review of systems and patients should be referred to a PCP or a mental health provider as needed.	100
Comorbidities and Treatment Selection	
NSAIDs may increase the risk for CVD and should be used with caution in this population. Patients with PsA and established CVD using NSAIDs should be counseled about this potential risk and NSAIDs should be avoided, if possible.	90
Avoid TNFi in patients with NYHA stage III or IV heart failure.	100
In patients with risk factors for VTE (ie, diabetes, treatment with corticosteroids, older age), consider avoiding the use of a JAKi.	100
Patients with obesity have a higher prevalence of fatty liver disease. For this reason, patients initiating MTX or LEF should be counseled on the increased probability of elevated LFTs with these medications and LFTs should be monitored more carefully in this population.	100
Avoid MTX or LEF in the setting of fatty liver disease.	90
Avoid MTX or LEF in the setting of active HBV or active HCV.	100
Avoid using TNFi in patients with PsA and MS and/or demyelinating disease.	100

CS: central sensitization; CV: cardiovascular; CVD: cardiovascular disease; FM: fibromyalgia; HBV: hepatitis B virus; HCV: hepatitis C virus; JAKi: Janus kinase inhibitor; LEF: leflunomide; LFT: liver function test; LTBI: latent tuberculosis infection; MS: multiple sclerosis; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; NYHA: New York Heart Association; PCP: primary care provider; PsA: psoriatic arthritis; QOL: quality of life; TB: tuberculosis; TNFi: tumor necrosis factor inhibitor; VTE: venous thromboembolism.

at an increased risk for the development of PsA.[35] The prevalence of depression is much higher in patients with PsA than in those with PsO but without PsA.[36] Data from the DANBIO registry showed that patients with depression and anxiety have higher disease activity scores at baseline and shorter persistence on treatment.[37] Depression is an important comorbidity and needs to be identified, diagnosed, and treated appropriately as it can lead to increased work disability, loss of income, and decreased health-related quality of life in patients with PsA. Appropriate psychiatric assessment and management are important.

Malignancies. The risk of development of malignancies in patients with PsA is low.[38] However, there is a relative dearth of information in this regard. In general, the rates of malignancy in patients with PsA are no different from that in the general population.[39-41] A previous study compared 8703 patients with spondyloarthritis (SpA), including PsA, commencing TNFi treatment between 2001 and 2011 with 28,164 TNFi-naïve patients with SpA, matched to a general population comparator cohort of 131,687 subjects.[42] It was found that TNFi was not associated with increased risks of cancer, neither overall nor for the 6 most common cancer types including prostate, lung, colorectal, breast, lymphoma, and melanoma.[42] Moreover, there was no increased risk of malignancy in the overall SpA population. Thus, PsA does not seem to be associated with an elevated risk of common malignancies in general. There are signals in trials and in cohort studies that nonmelanoma skin cancer may be elevated in patients using immunomodulatory medications.[43]

Osteoporosis. The inflammatory arthritides are generally associated with an increased risk of osteoporosis. However, unlike RA, where the link between RA and osteoporosis is well established, the literature is unclear about the risk of osteoporosis in patients with PsA. A cross-sectional study of an outpatient

population of patients with PsA showed that these patients were not at greater risk for the development of osteoporosis compared to the general population.[44] Therefore, the authors suggested that screening for osteoporosis in PsA should follow the same recommendations and guidelines as the general population. A Canadian longitudinal study cohort confirmed osteopenia in 45.3% and osteoporosis in 12.9% of patients with PsA, a prevalence similar to the general population.[45] Polyarticular disease was associated with worse bone mineral density, whereas biologic therapy and obesity seem to be protective against osteoporosis.[45] The above 2 studies suggest that osteoporosis is not a significant comorbidity in patients with PsA. However, patients with high disease activity, especially those with polyarticular disease, should have regular dual-energy x-ray absorptiometry monitoring. Recommendations/guidelines for osteoporosis surveillance should be the same in patients with PsA as those for the general population.

Multiple sclerosis. The data in the literature regarding the association of multiple sclerosis and PsO or PsA is contradictory. There are some studies which support the association while others do not.[46] TNFi are not recommended for use in patients with a personal history of demyelinating disease. On the other hand, there is a body of evidence that suggests the pathogenic role of IL-17 and Th17 in the development of multiple sclerosis and a previous proof-of-concept study found some mild benefit and did not demonstrate harm.[47]

Venous thromboembolic disease. There are several published studies which point to the increased risk of venous thromboembolism (VTE) in patients with PsO and PsA. However, the link between VTE and PsA is tenuous.[48] Obesity, CVD, increased platelet aggregation, NSAID use, and other traditional VTE risk factors in patients with PsA should be considered.

Fibromyalgia. FM and/or central sensitization affects approximately 20 to 30% of patients with PsA compared to approximately 6% of adults in the general population.[49] PROs including entheseal tenderness and the tender joint count, used in measuring disease activity of PsA, may be influenced by the presence of FM. For example, patients with FM consistently have higher PRO scores and entheseal tenderness regardless of the level of clinician-assessed disease activity. This is particularly important to recognize when applying a treat-to-target strategy, as patients with FM may be subject to overtreatment. In a patient with PsA and FM who has elevated PROs but an absence of joint swelling, switching therapies may not be appropriate. However, in a patient with FM and active PsA (ie, joint swelling is present), treatment selection should proceed as for any other patient with active PsA.

Vaccination. Because many of the therapies used to treat PsA are associated with an increased risk for infection, vaccinations can provide protection from some serious infections such as influenza, pneumonia, HZ, and coronavirus disease 2019 (COVID-19). In 2019, the European Alliance of Associations for Rheumatology (EULAR) updated vaccination recommendations for patients with autoimmune inflammatory rheumatic diseases.[50] In these recommendations, EULAR advocated for influenza, pneumococcal, HAV and HBV, and toxoid tetanus vaccinations.[50] Current recommendations suggest avoiding live vaccinations in patients who are immunosuppressed. For this reason, it is often best to encourage patients to get vaccinations prior to starting therapy as long as therapy will not be significantly delayed (ie, ideally 4 to 6 weeks before). Finally, we are still learning about the impact of therapies used to treat PsA on COVID-19 vaccination. The American College of Rheumatology (ACR) has published recommendations on vaccination for patients with rheumatic disease and will continue to update these recommendations as data accumulate.

Reproductive health. We have not focused on reproductive health in this article, but family planning should naturally be taken into account in therapy selection and solicited as a part of a comprehensive history. Several of our therapies are considered safe during pregnancy whereas others are harmful to the fetus, and some may be present in breast milk. The ACR recently released guidance for the management of reproductive health in rheumatic and musculoskeletal diseases.[51] This paper includes considerations for prescribing therapy during preconception, pregnancy, and lactation.

Research agenda. In reality, little evidence exists to inform the interactions between comorbidities and therapeutic interventions in PsA. There remains much to learn about comorbidities in the setting of PsA and the effect on treatment responses, as well as long-term outcomes. Suggestions for future research agendas (Table 4) should aim to identify the effect of modifying comorbidities on patient outcomes, develop adjunct therapies that improve PsA outcomes through treating comorbidities, develop methods for identifying and managing comorbidities, and improve understanding of the effect of comorbidities on treatment selection.

DISCUSSION

Comorbidities are important for understanding the "whole patient" with PsA sitting in front of us. They affect the patient's quality of life and in some cases, the quantity of life. Further, certain comorbidities impact either the effectiveness of a given therapy or the potential for AEs. In this evidence review, we examined the impact of individual comorbidities on treatment response and AEs as well as the potential opportunities to screen for individual comorbidities.

As a working group, we developed several key recommendations that were agreed upon by at least 90% of the group members. Enacting these recommendations in clinical practice begins with a comprehensive history and physical examination. Additional testing may then be carried out. As a group, we recognize that in clinical practice there may be barriers to carrying out all these recommendations, with lack of time being the most common and problematic. It is important to recognize that not all these recommendations need to be completed in a single visit, nor by a single clinician. It may be that most of the history is acquired on the first visit and screening takes place over the next several visits. Alternatively, it may be that the rheumatologist educates the patient and the primary care physician (PCP) that these screenings are recommended, and then the PCP addresses

Table 4. Suggested future research agendas for patients with PsA.

Comorbid Condition	Suggested Research Agendas
CV and metabolic disease	Ideal methods for CV risk screening in PsA Impact of disease activity and PsA therapies on CV risk Dietary changes and the microbiome impact on PsA disease activity and metabolic comorbidities Effect of modifying obesity and metabolic disease on response to therapy and overall disease activity Effect of fatty liver disease on PsA disease activity Treatment of fatty liver disease in PsA Methods for modifying CV risk in PsA
VTE	Risk for VTE on therapy among patients with PsA
Chronic pain, FM, depression and anxiety	Mental health and sleep and the impact on disease activity and therapy response Effect of FM on treatment outcomes and the best treatment options in the setting of PsA + FM Methods for assessing PsA disease activity in the setting of FM
Infections	COVID-19 in PsA and therapy outcomes Efficacy of herpes zoster vaccination in preventing herpes zoster in patients with PsA on JAKi
Vaccinations	Timing of vaccinations, which ones to prioritize, and the safety of vaccines in patients with PsA on therapy Effect of COVID-19 vaccination on disease activity Effect of therapy on vaccine response in PsA

COVID-19: coronavirus disease 2019; CV: cardiovascular; FM: fibromyalgia; JAKi: Janus kinase inhibitors; PsA: psoriatic arthritis; VTE: venous thromboembolism.

and manages the comorbidities once identified. Ideally, care of a patient with PsA is collaborative and involves the patient, the rheumatologist, the dermatologist, and the PCP (and/or cardiologist, hepatologist, infectious disease provider, etc.).

While there are strengths in this process, there are also limitations. The recommendations are only as strong as the data that form the basis for their formation. There remain knowledge gaps in the identification, management, and implications of comorbidities in PsA. Many studies have limited numbers of patients or limited follow-up and ultimately no clinical trials address the topics covered in this paper. There may be publication bias in the types of publications available for this review, including publications showing associations between PsA and the comorbidities studied. Regardless, the prevalence of these conditions is known to be elevated to such a degree that addressing these conditions remains important. There is much work to do to improve our understanding of how best to screen for, manage, and prevent comorbidities in patients with PsA.

In summary, we hope that the recommendations from the comorbidity working group will assist clinicians in identifying important comorbidities and considering their effects on treatment selection.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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