

Comprehensive Treatment of Psoriatic Arthritis: Managing Comorbidities and Extraarticular Manifestations

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ABSTRACT. Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis that can lead to decreased health-related quality of life and permanent joint damage leading to functional decline. In addition to joint and skin manifestations, both psoriasis and PsA are associated with numerous comorbidities and extraarticular/cutaneous manifestations, which may influence the physician's choice of therapy. The objectives of this review are (1) to identify comorbidities in patients with PsA based on the available evidence; (2) to examine the effects of these comorbidities or extraarticular/cutaneous manifestation on the management of patients with PsA as well as the selection of therapy; and (3) to highlight research needs around comorbidities and treatment paradigms. This review is part of a treatment recommendations update initiated by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). (J Rheumatol 2014;41:2315–22; doi:10.3899/jrheum.140882)

Key Indexing Terms:

CARDIOVASCULAR DISEASE OBESITY METABOLIC SYNDROME
DIABETES AUTOIMMUNE OPHTHALMIC DISEASE OSTEOPOROSIS

In this review, we discuss the most relevant comorbidities and highlight therapy options for patients with psoriatic arthritis (PsA).

Comorbidities

Cardiovascular disease (CVD). CVD such as an increased prevalence of ischemic heart disease, cerebrovascular disease, diastolic dysfunction, left ventricular dysfunction, abnormal carotid intimal thickness, and cardiovascular

death represent a major source of morbidity for patients with PsA^{1,2,3,4,5}. An increased prevalence of both novel and traditional risk factors including hypertension, obesity, diabetes mellitus (DM) and dyslipidemia, and smoking have also been found^{6,7,8}.

Obesity and metabolic syndrome. Obesity and metabolic syndrome have been observed with increased prevalence in patients with PsA; they may negatively affect disease activity and response to therapy^{9,10,11,12,13}.

Diabetes. Specifically, type II DM has been observed in 12%–18.6% of PsA patients¹⁴, partially explained by increased obesity and unhealthy lifestyle, and possibly related to insulin resistance driven by PsA inflammation^{15,16}.

Inflammatory bowel diseases (IBD). IBD including Crohn's disease and ulcerative colitis have been observed with increased incidence in patients with PsA (RR 6.54)¹⁷, and subclinical bowel inflammation has also been observed¹⁸.

Autoimmune ophthalmic disease. Autoimmune ophthalmic disease, including uveitis, keratitis, blepharitis, conjunctivitis, episcleritis, and scleritis, have been observed^{19,20,21}. The association with uveitis appears to be the strongest; in a metaanalysis, the prevalence of uveitis in PsA was 25.1%²².

Osteoporosis. Osteoporosis in patients with PsA was found to be similar to that in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), suggesting a higher prevalence of osteoporosis in PsA than previously thought^{23,24}.

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Malignancy. Malignancy may be associated with PsA although the data are inconsistent. Incidence rates in PsA (5.59/1000 patient-years of followup) were similar to those with rheumatoid arthritis (RA) in 1 study²⁵. In a recent population-based study, the average risk of lymphoma in PsA or AS was not elevated in contrast to RA²⁶.

Fatty liver disease. Fatty liver disease, particularly non-alcoholic fatty liver disease (NAFLD), has an increased prevalence in patients with psoriasis^{27,28,29}. Studies examining this relationship in patients with PsA are limited. Among patients with psoriasis, however, an increased prevalence of NAFLD is associated with metabolic syndrome, hypercholesterolemia, hypertriglyceridemia, obesity, psoriasis severity, and concomitant PsA^{28,29}.

Kidney disease. Kidney disease has been associated with psoriasis and PsA. Interestingly, patients with moderate-to-severe psoriasis had a higher risk of chronic kidney disease than the general population independent of traditional risk factors³⁰. Specific to PsA, the prevalence of reduced estimated glomerular filtration rate was 16% in patients with “seronegative arthritis” (patients with PsA and undifferentiated oligoarthritis), statistically similar to patients with RA (19%)³¹.

Additional Circumstances

Viral infection. Chronic viral infections such as hepatitis B and C (HBV, HCV) are particularly challenging in PsA patients and screening guidelines are limited. Treatment paradigms for PsA patients with inflammatory arthritis and HBV infection have not been established because of the potential for increased viral replication and/or reactivation with biologic medications³². Treatment recommendations for RA patients with concomitant HCV suggest that tumor necrosis factor inhibitors (TNFi) may be safe to use³³.

Vaccinations. Vaccinations in patients with PsA who may be taking immunosuppressive medications are recommended, preferably prior to initiation of certain immunosuppressive therapies³⁴. Recently published guidelines by the European League Against Rheumatism (EULAR) and the Advisory Committee on Immunization Practices (ACIP) have addressed this issue^{35,36}.

MATERIALS AND METHODS

In February 2013, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Treatment Recommendations group performed a centralized systematic literature search for articles published from 2003 (the year of the first GRAPPA systematic search) through early 2013 related to PsA, its manifestations, and therapies. The search was run in Medline and Embase and is described elsewhere³⁷. The Comorbidities Working Group performed additional searches for each comorbidity listed above, using terms common to each of these conditions.

RESULTS

Cardiovascular disease. As the management of PsA involves many disciplines, greater awareness regarding the

association of PsA and CVD is critical and should involve rheumatologists, cardiologists, dermatologists, and primary care physicians. Just as in the general population, traditional risk factors should be addressed, e.g., smoking cessation, treatment of hypertension and hyperlipidemias, and control of DM, when present. Additionally, recommended lifestyle changes include weight loss, decreased alcohol consumption for patients consuming excessively, increased physical activity, and a healthy well-balanced diet^{38,39}. Treatment targets for hypertension^{40,41} and hyperlipidemia are the same for patients with inflammatory arthritis as the general population. Of note, although management of lipids is changing for the general population^{42,43}, reanalysis of clinical data of 1 study showed that patients with inflammatory arthritis (199 with RA, 46 with AS, and 35 with PsA) treated with intensive statins had a similar decline in lipid levels and a 20% reduction in overall risk of CVD as patients without inflammatory arthritis⁴⁴.

The “psoriatic march” suggests that systemic inflammation (e.g., elevated cytokines such as TNF- α) leads to increased insulin resistance, oxidative stress, endothelial cell dysfunction, and the development of atherosclerosis, which ultimately results in myocardial infarction (MI) or cerebrovascular accidents (CVA)⁴⁵. Thus, decreasing inflammation through the use of disease-modifying anti-rheumatic drugs (DMARD) has been hypothesized to attenuate CV risk. Several studies of the effects of TNFi on carotid intima media thickness (CMT), aortic stiffness measured by aortic pulse wave velocity, adipokine levels, platelet reactivity, and postocclusion flow-mediated vasodilatation have suggested possible favorable effects of TNFi in PsA and psoriasis⁵. Although few studies have examined the effect of non-biologic DMARD on CVD in PsA patients, 1 study of an early RA cohort demonstrated a significant reduction in CMT after 1 year of therapy with methotrexate (MTX), sulfasalazine, hydroxychloroquine, or a combination of these therapies⁴⁶.

To date, no prospective studies have specifically examined the effect of aggressive PsA treatment regimens on risk of cardiovascular events. Randomized controlled trials (RCT) of TNFi in psoriasis and PsA have not shown significant differences in risk of CV events although timespans of these studies have been short^{47,48,49,50}. Large RCT with longterm followup should be done but would be expensive and difficult to conduct.

More recent therapeutics for psoriatic diseases include a phosphodiesterase-4 inhibitor (apremilast) and interleukin 12/23 (IL-12/23) antagonists (i.e., ustekinumab and briakinumab). Initial studies of IL-12/23 antagonists in patients with psoriasis raised concern about increased risks of MI, CVA, and arrhythmia. Development of briakinumab was halted in the US and Europe in 2011 due to concerns about increased CVD, malignancy, and serious infection^{51,52}. Two recent metaanalyses examining CV events in the IL-12/23

antagonists among psoriasis patients (PsA patients were excluded) resulted in different conclusions: Ryan, *et al* showed a combined risk difference for ustekinumab and briakinumab of 0.012⁵³, and Tzellos, *et al* found a pooled odds ratio of 4.23⁵⁴. Differences in methodology may have played a role in the differing results⁵¹.

In patients with concurrent CVD, there is no specific recommendation for a particular DMARD that would attenuate CV risk. Studies specific to patients with PsA have not examined their risk of CV outcomes associated with nonsteroidal antiinflammatory drugs (NSAID) and corticosteroids.

Congestive heart failure (CHF) may sometimes complicate treatment of PsA. In a trial of infliximab (TNFi) for CHF, some patients (without rheumatic diseases) had increased hospital admissions for CHF exacerbations and increased mortality⁵⁵; however, most cardiovascular deaths occurred after therapy, not during the short treatment protocol. Although RCT of TNFi in inflammatory arthritis have excluded patients with CHF, observational studies have suggested no significant effect on new diagnosis of CHF among RA patients receiving TNFi^{56,57}.

Obesity. Being overweight (BMI > 25) or obese (BMI > 30) has been associated with psoriasis and PsA. Although no significant data suggest weight gain or loss with traditional DMARD, results have been variable among studies examining TNFi. Some show body weight increased after treatment with TNFi^{58,59,60} although generally the weight gained is minimal⁵⁹. A recent prospective study found no significant change in weight at 24 months⁶¹. A retrospective study demonstrated that metabolic syndrome components (waist circumference, triglycerides, high-density lipoprotein cholesterol, and glucose) improved significantly among PsA patients treated with adalimumab or etanercept compared to those receiving MTX alone⁶².

In PsA, there is an implication that obesity affects response to therapy. A prospective study found that obesity was associated with a hazard ratio of 4.9 for not achieving minimal disease activity (MDA)⁶¹. In patients who achieved MDA at 12 months, obesity was a significant risk factor for relapse at 24 months^{61,63}. The presence of metabolic syndrome was also a risk factor for not achieving MDA⁶⁴. Finally, obesity may also be a risk factor for liver fibrosis in patients with moderate to severe psoriasis⁶⁵. Lower body weight and weight loss have been associated with beneficial therapeutic effects for both TNFi and cyclosporine in psoriasis patients^{58,66}.

Diabetes. DM is a relatively prevalent comorbidity among patients with PsA compared to the general population¹⁴, although data are limited. The use of oral and topical corticosteroids in an observational study increased the risk of developing DM by 30% in patients with psoriatic disease, while the use of TNFi was associated with a reduced risk of

developing DM (OR 0.62) compared to the use of other non-biologic DMARD (excluding MTX)^{67,68}.

Inflammatory bowel disease. Given the overlap with the spondyloarthropathies, knowledge about the prevalence and spectrum of IBD is important, particularly as the associated potential morbidity of the co-occurrence of IBD with PsA is high. The data to support the association of IBD with PsA are sparse, comprising small case reports and series^{69,70}. Treatment choices for patients with concurrent PsA/IBD should be made carefully, with consideration for the systemic disease, dermal, musculoskeletal, and gastro-intestinal manifestations, and the risk and benefits of available therapies. Therapies used to treat IBD may overlap with medications used to treat PsA. Common medications for IBD include aminosalicylates, corticosteroids, metronidazole, ciprofloxacin, 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, MTX, infliximab, adalimumab, golimumab, certolizumab, and natalizumab⁷¹. Occasionally, patients may develop IBD, uveitis, or psoriasis when being treated with an anti-TNF agent. Because case numbers are so small, a causative role cannot be associated with the use of anti-TNF agents in PsA patients who develop these conditions^{72,73,74}.

No data have been published assessing the appropriate therapy for concomitant PsA and IBD. Similarly, there are no clear guidelines regarding use of NSAID in patients with IBD as it is unclear whether NSAID may exacerbate IBD symptoms^{75,76}.

Autoimmune ophthalmic disease. The prevalence and spectrum of autoimmune ophthalmic disease in PsA is significant and the associated potential morbidity is high^{19,77}. Therefore, PsA patients with ophthalmic symptoms should be evaluated early. The ophthalmic manifestations of PsA include uveitis, keratitis, blepharitis, conjunctivitis, episcleritis, and scleritis^{19,20,21}. Autoimmune ophthalmic disease can precede PsA or occur after the onset of PsA.

Available data support the use of corticosteroids (systemic, periocular, and implants), MTX, mycophenolate, cyclosporine, azathioprine, and some of the anti-TNF agents to treat patients with uveitis^{78,79}. The 2 most frequently used biologic agents are infliximab and adalimumab, and adalimumab was recently granted orphan status for the treatment of some forms of uveitis^{80,81}. Etanercept may not adequately treat uveitis⁸².

Osteoporosis. A high index of suspicion for osteoporosis should be maintained in patients with PsA, as complications of undertreated osteoporosis can be devastating. In PsA patients using glucocorticoids, standard guidelines for the prevention of glucocorticoid-induced osteoporosis should be followed⁸³.

Limited data examine the effect of osteoporosis medications on PsA disease activity and outcomes. In one pilot study, however, the effect of zoledronic acid on articular bone in patients with PsA demonstrated suppression of bone

marrow edema on magnetic resonance imaging and improvement in clinical outcomes⁸⁴. In an RA study, improvement in bone density was suggested with low-dose MTX, sulfasalazine, and TNFi⁸⁵.

Malignancy. The risk of malignancy in patients with PsA is unclear as the published data are insufficient and conflicting. In general, the incidence rates do not differ from the general population^{86,87}. In a metaanalysis of RCT across all indications, short-term use of TNFi was not associated with a significantly increased risk of cancer⁸⁸. However, an increase in non-melanoma skin cancers (70.6% of malignancies in the analysis) was observed in patients using TNFi (OR 1.33, 95% CI 0.58–3.04; incidence rate ratio 0.72). When stratified by disease, PsA patients had no increased risk for malignancy (OR 0.83). Concomitant immunosuppressive therapy use was notably lower in the 7 included PsA trials (1485 patients) compared to previous RA studies (44.6% on MTX, 5.5% on another DMARD, and 10.5% on corticosteroids at baseline). Similarly, an observational study examined the risk for solid malignancy among patients with PsA using TNFi compared to patients receiving non-biologic regimens in US-based Medicare and Medicaid databases. Among 2498 patients with PsA, the HR for incident solid cancer diagnosis was 0.74 (95% CI 0.20–2.76)⁸⁹. Limited studies have addressed the risk of melanoma in patients with PsA.

The introduction of TNFi for treating PsA has raised some challenges. It remains unclear if patients with PsA and a history of cancer would be at greater risk of recurrent cancer if administered these agents. One study conducted in the British Society for Rheumatology Biologics Registry among 238 RA patients with previous carcinoma *in situ* of the cervix showed no significant increased risk of incident female genital cancers (0 in the TNF group, 2 in the non-biologic DMARD group over 893 and 159 person-years, respectively)⁹⁰.

Liver disease. Liver disease can result from the disease itself as well as the medications used to treat PsA, and the presence of liver disease can complicate therapy selection in PsA. In RA patients, NSAID may be associated with liver function test (LFT) abnormalities and hepatotoxicity⁹¹, and TNFi have been associated with LFT abnormalities⁹². However, patients with PsA treated with combination TNFi/MTX had a lower risk of liver fibrosis than patients treated with MTX alone⁹³. In another study, LFT were not significantly elevated in PsA patients using MTX or TNFi compared to nonusers, but prior liver disease was associated with LFT abnormalities in all groups⁹⁴.

MTX and leflunomide have been associated with elevated LFT as well as with development of nonalcoholic steatohepatitis (NASH)/NAFLD and/or cirrhosis. Higher rates of NASH/NAFLD may occur in patients with PsA using MTX compared to those with RA⁹³, and LFT abnormalities may be similar or slightly higher in PsA^{95,96,97}.

Studies in psoriasis may be informative: development of NASH/NAFLD in longterm users of MTX was associated with cumulative MTX dose as well as presence of obesity or DM^{98,99}.

Few studies have addressed the influence of therapies for PsA on existing liver disease. In a study examining the relationship between hepatic steatosis, disease activity, and use of TNFi¹⁰⁰, patients with PsA who achieved MDA after treatment with a TNFi had an equivalent risk of worsening of hepatic steatosis compared to those in the control group, and a lower risk of worsening steatosis than PsA patients taking TNFi who did not achieve MDA.

Kidney disease. Given the potential effect of chronic kidney disease (CKD) in patients with moderate-to-severe psoriasis and the effect of therapy on renal function, this potential comorbidity should be considered in patients with PsA. Evidence is limited on use of immunosuppressive agents in patients with CKD or endstage renal disease. Patients receiving dialysis present an additional challenge. One study demonstrated that leflunomide may be used in RA patients on hemodialysis¹⁰¹. MTX is not cleared well by hemodialysis so the risk for pancytopenia is increased¹⁰². Etanercept was well tolerated in 5 patients with RA or SpA¹⁰³.

Nephrotoxicity may be a concern with some medications. Nephrotoxicity in cyclosporine users with psoriasis was associated with longer use, larger cumulative dose, and higher daily dose¹⁰⁴. NSAID may increase the risk for acute renal failure in patients with CKD¹⁰⁵.

Additional Circumstances

Chronic viral infections. Chronic viral infections such as HCV, HBV, and human immunodeficiency virus (HIV) may have implications for therapy choice in patients with PsA. The use of potentially hepatotoxic and immunosuppressive drugs requires caution given the potential for increased viral replication. Patients with rheumatic diseases and chronic HBV infection have a high frequency of reactivation of HBV with biologic treatment¹⁰⁶, although data are limited in patients with PsA. Among patients with rheumatic, dermatologic, and digestive diseases treated with anti-TNF agents, HBV reactivation occurred in 25% of those who received antiviral therapy compared to 62% in those who did not³². Screening for HBV (as well as HCV and HIV) should be performed before beginning an immunosuppressive agent³⁴.

Vaccinations. Given the increased risk of infection among users of immunosuppressive medications, vaccinations are often a concern among patients with PsA. While there are no specific guidelines for PsA, it would be reasonable to follow the general guidelines for vaccinations from organizations such as the ACIP, American College of Rheumatology, and EULAR^{35,36}.

In this review, we have highlighted the association of PsA with multiple comorbidities and extraarticular/

cutaneous manifestations. As care providers, it is important that we be aware of these associations in order to improve the comprehensive management of PsA patients. While there is much debate over who should directly manage these comorbidities, patients benefit from communication and education by both primary care providers and specialists.

Significant gaps remain in both our understanding of the associations of these comorbidities and extraarticular/cutaneous manifestations and their implications for therapy selection in PsA patients (Table 1). As new medications are added to the available PsA therapies, it will be important to study their effects on comorbidities and extraarticular/dermal manifestations, so that we may provide more tailored treatment options for our patients with PsA.

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Table 1. Future research needs.

Comorbidity/Circumstance	Future Research
Cardiovascular disease	Develop risk models for CVD among PsA patients (and patients with inflammatory arthritis in general) Examine the effect of therapies on the risk for CV outcomes (ideally in a prospective RCT) Examine the effects of ustekinumab on CV outcomes in PsA patients Examine the safety of biologic DMARD in patients with CHF and PsA
Obesity	Define association between obesity and development of PsA and whether this risk is mitigated by weight loss Examine the effect of weight loss on disease activity in PsA Examine the safety of MTX and leflunomide in obese patients with PsA Examine the effect of regular exercise on disease activity measures
Diabetes	Examine the effect of therapy on blood glucose control in patients with PsA and diabetes Examine the effect of optimal glucose control on disease activity in PsA patients Examine the safety of MTX and leflunomide in patients with PsA and diabetes Examine the effect of therapy on the risk for development of diabetes in PsA patients
Inflammatory bowel disease	Define association of IBD and PsA in large cohort studies Examine appropriate therapy selection for patients with PsA and IBD
Ophthalmic disease	Define association of uveitis and PsA in large cohort studies Examine appropriate therapy selection for patients with PsA and ophthalmic disease
Osteoporosis	Define association of osteoporosis and PsA in large cohort studies Examine the effect of therapy for osteoporosis on disease activity in PsA Examine the effect of therapy for PsA on development of osteoporosis
Malignancy	Define risk of malignancy (including skin cancer) among PsA patients and better define the risk of malignancy with use of therapies for PsA
Fatty liver disease	Define the prevalence of fatty liver disease among PsA patients and the association with disease activity Examine the effect of therapies for PsA on fatty liver disease
Kidney disease	Examine safety of therapies for PsA in patients with chronic kidney disease
Chronic viral infections	Examine safety of therapies for PsA in patients with chronic HBV, HCV, and HIV
Vaccinations	Define the best timing and ideal vaccination regimens in patients with PsA

PsA: psoriatic arthritis; CVD: cardiovascular disease; IBD: inflammatory bowel disease; HBV/HCV: hepatitis B/C virus; HIV: human immunodeficiency virus.

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