Comprehensive Treatment of Psoriatic Arthritis: Managing Comorbidities and Extraarticular Manifestations

Alexis Ogdie, Sergio Schwartzman, Lihi Eder, Ajesh B. Maharaj, Devy Zisman, Siba P. Raychaudhuri, Soumya M. Reddy, and Elaine Husni

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 extra-articular/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 patients[14], 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 observed[18].

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].

From the University of Pennsylvania, Philadelphia, Pennsylvania; Hospital for Special Surgery, New York, New York, USA; Toronto Western Hospital, Toronto, Ontario, Canada; Nelson R. Mandela School of Medicine, University of KwaZulu Natal, Durban, South Africa, and Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Carmel Medical Center, Faculty of Medicine, Technion, Haifa, Israel; Rheumatology, VA Sacramento Medical Center; Division of Rheumatology, Allergy and Clinical Immunology, School of Medicine, UC Davis, Davis, California; Division of Rheumatology, New York University School of Medicine, New York, New York; and the Cleveland Clinic, Cleveland, Ohio, USA.

A. Ogdie, MD, MSCE, University of Pennsylvania; S. Schwartzman, MD, Hospital for Special Surgery; L. Eder, MD, PhD, Toronto Western Hospital; A.B. Maharaj, MB, BS, HDipIntMed(SA), FCP(SA), Nelson R. Mandela School of Medicine, University of KwaZulu Natal and Academic Medical Center, University of Amsterdam; D. Zisman, MD, Carmel Medical Center, Faculty of Medicine, Technion; S.P. Raychaudhuri, MD, Rheumatology, VA Sacramento Medical Center; Division of Rheumatology, Allergy and Clinical Immunology, School of Medicine, UC Davis; S.M. Reddy, MD, Division of Rheumatology, New York University School of Medicine; E. Husni, MD, MPH, Cleveland Clinic.

Address correspondence to Dr. E. Husni, Rheumatologic and Immunologic Disease, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. E-mail: HUSNIE@ccf.org

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 study[25]. In a recent population-based study, the average risk of lymphoma in PsA or AS was not elevated in contrast to RA[26].

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 factors[30]. 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 medications[32]. Treatment recommendations for RA patients with concomitant HCV suggest that tumor necrosis factor inhibitors (TNFi) may be safe to use[33].

Vaccinations. Vaccinations in patients with PsA who may be taking immunosuppressive medications are recommended, preferably prior to initiation of certain immunosuppressive therapies[34]. 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 elsewhere[37]. 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 arthritis[44].

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 antirheumatic drugs (DMARD) has been hypothesized to attenuate CV risk. Several studies of the effects of TNFi on carotid intima media thickness (CIMT), 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 psoriasis[5]. 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 CIMT after 1 year of therapy with methotrexate (MTX), sulfasalazine, hydroxychloroquine, or a combination of these therapies[46].

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 0.012[53], and Tzellos, *et al* found a pooled odds ratio of 4.23[54]. Differences in methodology may have played a role in the differing results[51].

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 mortality[55]; 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 minimal[59]. A recent prospective study found no significant change in weight at 24 months[61]. 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 alone[62].

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 MDA[64]. Finally, obesity may also be a risk factor for liver fibrosis in patients with moderate to severe psoriasis[65]. 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 population[14], 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 natalizumab[71]. 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 uveitis[82].

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 followed[83].

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 outcomes[84]. In an RA study, improvement in bone density was suggested with low-dose MTX, sulfasalazine, and TNFi[85].

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 cancer[88]. 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 hepatotoxicity[91], and TNFi have been associated with LFT abnormalities[92]. However, patients with PsA treated with combination TNFi/MTX had a lower risk of liver fibrosis than patients treated with MTX alone[93]. 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 groups[94].

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 RA[93], 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 TNFi[100], 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 hemodialysis[101]. MTX is not cleared well by hemodialysis so the risk for pancytopenia is increased[102]. Etanercept was well tolerated in 5 patients with RA or SpA[103].

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 dose[104]. NSAID may increase the risk for acute renal failure in patients with CKD[105].

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 treatment[106], 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 not[32]. Screening for HBV (as well as HCV and HIV) should be performed before beginning an immunosuppressive agent[34].

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.

REFERENCES

1. Shang Q, Tam LS, Sanderson JE, Sun JP, Li EK, Yu CM. Increase in ventricular-arterial stiffness in patients with psoriatic arthritis. Rheumatology 2012;51:2215-23.
2. Shang Q, Tam LS, Yip GW, Sanderson JE, Zhang Q, Li EK, et al. High prevalence of subclinical left ventricular dysfunction in patients with psoriatic arthritis. J Rheumatol 2011;38:1363-70.
3. Eder L, Jayakar J, Shanmugarajah S, Thavaneswaran A, Pereira D, Chandran V, et al. The burden of carotid artery plaques is higher in patients with psoriatic arthritis compared with those with psoriasis alone. Ann Rheum Dis 2013;72:715-20.
4. Lin YC, Dalal D, Churton S, Brennan DM, Korman NJ, Kim ES, et al. Relationship between metabolic syndrome and carotid intima-media thickness: Cross-sectional comparison between psoriasis and psoriatic arthritis. Arthritis Care Res 2014;66:97-103.
5. Jamnitski A, Symmons D, Peters MJ, Sattar N, McInnes I, Nurmohamed MT. Cardiovascular comorbidities in patients with psoriatic arthritis: A systematic review. Ann Rheum Dis 2013;72:211-6.
6. Husted JA, Thavaneswaran A, Chandran V, Eder L, Rosen CF, Cook RJ, et al. Cardiovascular and other comorbidities in patients with psoriatic arthritis: A comparison with patients with psoriasis. Arthritis Care Res 2011;63:1729-35.
7. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: A systematic review and meta-analysis of observational studies. J Hypertens 2013;31:433-43.
8. Armstrong AW, Harskamp CT, Dhillon JS, Armstrong EJ. Psoriasis and smoking: A systematic review and meta-analysis. Br J Dermatol 2014;170:304-14.
9. Li W, Han J, Qureshi AA. Obesity and risk of incident psoriatic arthritis in US women. Ann Rheum Dis 2012;71:1267-72.
10. Kumar S, Han J, Li T, Qureshi AA. Obesity, waist circumference, weight change and the risk of psoriasis in US women. J Eur Acad Dermatol Venereol 2013;27:1293-8.
11. Love TJ, Zhu Y, Zhang Y, Wall-Burns L, Ogdie A, Gelfand JM, et al. Obesity and the risk of psoriatic arthritis: A population-based study. Ann Rheum Dis 2012;71:1273-7.
12. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol 2010;146:721-6.
13. Sharma A, Gopalakrishnan D, Kumar R, Vijayvergiya R, Dogra S. Metabolic syndrome in psoriatic arthritis patients: A cross-sectional study. Int J Rheum Dis 2013;16:667-73.
14. Dreiher J, Freud T, Cohen AD. Psoriatic arthritis and diabetes: A

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.

population-based cross-sectional study. Dermatol Res Pract 2013;2013:580404.
15. Coto-Segura P, Eiris-Salvado N, Gonzalez-Lara L, Queiro-Silva R, Martinez-Camblor P, Maldonado-Seral C, et al. Psoriasis, psoriatic arthritis and type 2 diabetes mellitus: A systematic review and meta-analysis. Br J Dermatol 2013;169:783-93.
16. Boehncke S, Salgo R, Garbaraviciene J, Beschmann H, Hardt K, Diehl S, et al. Effective continuous systemic therapy of severe plaque-type psoriasis is accompanied by amelioration of biomarkers of cardiovascular risk: Results of a prospective longitudinal observational study. J Eur Acad Dermatol Venereol 2011;25:1187-93.
17. Li WQ, Han JL, Chan AT, Qureshi AA. Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. Ann Rheum Dis 2013;72:1200-5.
18. Scarpa R, Manguso F, D'Arienzo A, D'Armiento FP, Astarita C, Mazzacca G, et al. Microscopic inflammatory changes in colon of patients with both active psoriasis and psoriatic arthritis without bowel symptoms. J Rheumatol 2000;27:1241-6.
19. Lambert JR, Wright V. Eye inflammation in psoriatic arthritis. Ann Rheum Dis 1976;35:354-6.
20. Altan-Yaycioglu R, Akova YA, Kart H, Cetinkaya A, Yilmaz G, Aydin P. Posterior scleritis in psoriatic arthritis. Retina 2003;23:717-9.
21. Lima FB, Abalem MF, Ruiz DG, Gomes Bde A, Azevedo MN, Moraes HV Jr, et al. Prevalence of eye disease in Brazilian patients with psoriatic arthritis. Clinics (Sao Paulo) 2012;67:249-53.
22. Zeboulon N, Dougados M, Gossec L. Prevalence and characteristics of uveitis in the spondyloarthropathies: A systematic literature review. Ann Rheum Dis 2008;67:955-9.
23. Reddy SM, Anandarajah AP, Fisher MC, Mease PJ, Greenberg JD, Kremer JM, et al. Comparative analysis of disease activity measures, use of biologic agents, body mass index, radiographic features, and bone density in psoriatic arthritis and rheumatoid arthritis patients followed in a large U.S. disease registry. J Rheumatol 2010;37:2566-72.
24. Teichmann J, Voglau MJ, Lange U. Antibodies to human tissue transglutaminase and alterations of vitamin D metabolism in ankylosing spondylitis and psoriatic arthritis. Rheumatol Int 2010;30:1559-63.
25. Gross R, Schwartzman-Morris J, Krathen M, Reed G, Chang H, Saunders KC, et al. The risk of malignancy in a large cohort of patients with psoriatic arthritis [abstract]. Arthritis Rheum 2011;63 Suppl:S195.
26. Hellgren K, Smedby K, Baecklund E. Ankylosing spondylitis, psoriatic arthritis and risk of malignant lymphoma: A cohort study based on nationwide prospectively recorded data from Sweden. Arthritis Rheum 2014;66:1282-90.
27. Madanagobalane S, Anandan S. The increased prevalence of non-alcoholic fatty liver disease in psoriatic patients: A study from South India. Australas J Dermatol 2012;53:190-7.
28. Miele L, Vallone S, Cefalo C, La Torre G, Di Stasi C, Vecchio FM, et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009;51:778-86.
29. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009;51:758-64.
30. Wan J, Wang S, Haynes K, Denburg MR, Shin DB, Gelfand JM. Risk of moderate to advanced kidney disease in patients with psoriasis: Population based cohort study. BMJ 2013;347:f5961.
31. Haroon M, Adeeb F, Devlin J, O Gradaigh D, Walker F. A comparative study of renal dysfunction in patients with inflammatory arthropathies: Strong association with cardiovascular diseases and not with anti-rheumatic therapies, inflammatory markers or duration of arthritis. Int J Rheum Dis 2011;14:255-60.
32. Perez-Alvarez R, Diaz-Lagares C, Garcia-Hernandez F, Lopez-Roses L, Brito-Zeron P, Perez-de-Lis M, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: Analysis of 257 cases. Medicine (Baltimore) 2011;90:359-71.
33. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.
34. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:e44-100.
35. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;70:414-22.
36. Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedule for Adults Aged 19 Years and Older — United States, 2013. 2013 [Internet; accessed August 7, 2014.]; Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a3.htm
37. Coates LC, Kavanaugh A, Ritchlin CT, for the GRAPPA Treatment Guideline Committee. Systematic review of treatments for psoriatic arthritis: 2014 update. J Rheumatol 2014;41:2273-6.
38. American Heart Association, Diet and Lifestyle Recommendations 2014 [Internet. Accessed August 7, 2014]; Available from: http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/HealthyEating/The-American-Heart-Associations-Diet-and-Lifestyle-Recommendations_UCM_305855_Article.jsp
39. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635-701.
40. Recarti C, Unger T. Prevention of coronary artery disease: Recent advances in the management of hypertension. Curr Atheroscler Rep 2013;15:311.
41. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
42. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769-818.
43. Stone NJ, Robinson JG, Lichtenstein AH, Goff DC Jr, Lloyd-Jones DM, Smith SC Jr, et al; 2013 ACC/AHA Cholesterol Guideline Panel. Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline. Ann Intern Med 2014;160:339-43.
44. Semb AG, Kvien TK, DeMicco DA, Fayyad R, Wun CC, LaRosa JC, et al. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. Arthritis Rheum 2012;64:2836-46.
45. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': A concept of how severe psoriasis may drive cardiovascular comorbidity. Exp Dermatol 2011;20:303-7.

46. Guin A, Chatterjee Adhikari M, Chakraborty S, Sinhamahapatra P, Ghosh A. Effects of disease modifying anti-rheumatic drugs on subclinical atherosclerosis and endothelial dysfunction which has been detected in early rheumatoid arthritis: 1-year follow-up study. Semin Arthritis Rheum 2013;43:48-54.
47. Chen YJ, Chang YT, Shen JL, Chen TT, Wang CB, Chen CM, et al. Association between systemic antipsoriatic drugs and cardiovascular risk in patients with psoriasis with or without psoriatic arthritis: A nationwide cohort study. Arthritis Rheum 2012;64:1879-87.
48. Lan CC, Ko YC, Yu HS, Wu CS, Li WC, Lu YW, et al. Methotrexate reduces the occurrence of cerebrovascular events among Taiwanese psoriatic patients: A nationwide population-based study. Acta Derm Venereol 2012;92:349-52.
49. Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. Arch Dermatol 2012;148:1244-50.
50. Wu JJ, Poon KY, Bebchuk JD. Association between the type and length of tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. J Drugs Dermatol 2013;12:899-903.
51. Dommasch ED, Troxel AB, Gelfand JM. Major cardiovascular events associated with anti-IL 12/23 agents: A tale of two meta-analyses. J Am Acad Dermatol 2013;68:863-5.
52. Lebwohl M. Interleukin 12/23 agents and major adverse cardiovascular events. Arch Dermatol 2012;148:1329.
53. Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: A meta-analysis of randomized controlled trials. JAMA 2011;306:864-71.
54. Tzellos T, Kyrgidis A, Zouboulis CC. Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: A meta-analysis of randomized controlled trials. J Eur Acad Dermatol Venereol 2013;27:622-7.
55. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: Results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133-40.
56. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: Rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med 2004;116:305-11.
57. Jain A, Singh JA. Harms of TNF inhibitors in rheumatic diseases: A focused review of the literature. Immunotherapy 2013;5:265-99.
58. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: A retrospective cohort study. J Eur Acad Dermatol Venereol 2008;22:341-4.
59. Prignano F, Ricceri F, Pescitelli L, Buggiani G, Troiano M, Zanieri F, et al. Comparison of body weight and clinical-parameter changes following the treatment of plaque psoriasis with biological therapies. Curr Med Res Opin 2009;25:2311-6.
60. Saraceno R, Schipani C, Mazzotta A, Esposito M, Di Renzo L, De Lorenzo A, et al. Effect of anti-tumor necrosis factor-alpha therapies on body mass index in patients with psoriasis. Pharmacol Res 2008;57:290-5.
61. di Minno MN, Peluso R, Iervolino S, Lupoli R, Russolillo A, Scarpa R, et al. Obesity and the prediction of minimal disease activity: A prospective study in psoriatic arthritis. Arthritis Care Res 2013;65:141-7.
62. Costa L, Caso F, Atteno M, Del Puente A, Darda MA, Caso P, et al. Impact of 24-month treatment with etanercept, adalimumab, or methotrexate on metabolic syndrome components in a cohort of 210 psoriatic arthritis patients. Clin Rheumatol 2014;33:833-9.
63. Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. Ann Rheum Dis 2014 Jan 15 [Epub ahead of print]
64. Di Minno MN, Peluso R, Iervolino S, Lupoli R, Russolillo A, Tarantino G, et al. Hepatic steatosis, carotid plaques and achieving MDA in psoriatic arthritis patients starting TNF-alpha blockers treatment: A prospective study. Arthritis Res Ther 2012;14:R211.
65. Montaudie H, Sbidian E, Paul C, Maza A, Gallini A, Aractingi S, et al. Methotrexate in psoriasis: A systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. J Eur Acad Dermatol Venereol 2011;25 Suppl 2:12-8.
66. Cassano N, Galluccio A, De Simone C, Loconsole F, Massimino SD, Plumari A, et al. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: An exploratory analysis from the APHRODITE data. J Biol Regul Homeost Agents 2008;22:233-7.
67. Solomon DH, Love TJ, Canning C, Schneeweiss S. Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. Ann Rheum Dis 2010;69:2114-7.
68. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA 2011;305:2525-31.
69. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: A population-based study. Gastroenterology 2005;129:827-36.
70. Yates VM, Watkinson G, Kelman A. Further evidence for an association between psoriasis, Crohn's disease and ulcerative colitis. Br J Dermatol 1982;106:323-30.
71. Talley NJ, Abreu MT, Achkar JP, Bernstein CN, Dubinsky MC, Hanauer SB, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol 2011;106 Suppl 1:S2-25; quiz S6.
72. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum 2007;56:3248-52.
73. Cleynen I, Vermeire S. Paradoxical inflammation induced by anti-TNF agents in patients with IBD. Nat Rev Gastroenterol Hepatol 2012;9:496-503.
74. Fiorino G, Danese S, Pariente B, Allez M. Paradoxical immune-mediated inflammation in inflammatory bowel disease patients receiving anti-TNF-alpha agents. Autoimmun Rev 2014;13:15-9.
75. Bonner GF, Walczak M, Kitchen L, Bayona M. Tolerance of nonsteroidal antiinflammatory drugs in patients with inflammatory bowel disease. Am J Gastroenterol 2000;95:1946-8.
76. Felder JB, Korelitz BI, Rajapakse R, Schwarz S, Horatagis AP, Gleim G. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: A case-control study. Am J Gastroenterol 2000;95:1949-54.
77. Au SC, Yaniv S, Gottleib A. Psoriatic eye manifestations. Psoriasis Forum 2011;17:169-79.
78. Servat JJ, Mears KA, Black EH, Huang JJ. Biological agents for the treatment of uveitis. Expert Opin Biol Ther 2012;12:311-28.
79. Kruh J, Foster CS. The philosophy of treatment of uveitis: Past, present and future. Dev Ophthalmol 2012;51:1-6.
80. Martel JN, Esterberg E, Nagpal A, Acharya NR. Infliximab and adalimumab for uveitis. Ocul Immunol Inflamm 2012;20:18-26.
81. Zannin ME, Birolo C, Gerloni VM, Miserocchi E, Pontikaki I, Paroli MP, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. J Rheumatol 2013;40:74-9.

82. Smith JA, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum 2005;53:18-23.
83. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res 2010;62:1515-26.
84. McQueen F, Lloyd R, Doyle A, Robinson E, Lobo M, Exeter M, et al. Zoledronic acid does not reduce MRI erosive progression in PsA but may suppress bone oedema: The Zoledronic Acid in Psoriatic Arthritis (ZAPA) Study. Ann Rheum Dis 2011;70:1091-4.
85. Dimitroulas T, Nikas SN, Trontzas P, Kitas GD. Biologic therapies and systemic bone loss in rheumatoid arthritis. Autoimmun Rev 2013;12:958-66.
86. Rohekar S, Tom BD, Hassa A, Schentag CT, Farewell VT, Gladman DD. Prevalence of malignancy in psoriatic arthritis. Arthritis Rheum 2008;58:82-7.
87. Ogdie A, Maliha S, Love T, Choi H, Gelfand J. Cause-specific mortality in patients with psoriatic arthritis [abstract]. Ann Rheum Dis 2013;72 Suppl 3:519.
88. Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: A systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol 2011;64:1035-50.
89. Haynes K, Beukelman T, Curtis JR, Newcomb C, Herrinton LJ, Graham DJ, et al. Tumor necrosis factor alpha inhibitor therapy and cancer risk in chronic immune-mediated diseases. Arthritis Rheum 2013;65:48-58.
90. Mercer LK, Low AS, Galloway JB, Watson KD, Lunt M, Symmons DP, et al. Anti-TNF therapy in women with rheumatoid arthritis with a history of carcinoma in situ of the cervix. Ann Rheum Dis 2013;72:143-4.
91. O'Connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. QJM 2003;96:787-91.
92. Sokolove J, Strand V, Greenberg JD, Curtis JR, Kavanaugh A, Kremer JM, et al. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:1612-7.
93. Seitz M, Reichenbach S, Moller B, Zwahlen M, Villiger PM, Dufour JF. Hepatoprotective effect of tumour necrosis factor alpha blockade in psoriatic arthritis: A cross-sectional study. Ann Rheum Dis 2010;69:1148-50.
94. Kavanaugh A, Greenberg J, Lee S, Need B, Moreland LW. Incidence of elevated liver enzymes (LFTS) in psoriatic arthritis (PsA) patients: Effect of TNF-inhibitors (TNF-I) [abstract]. Ann Rheum Dis 2010;69 Suppl:579.
95. Amital H, Arnson Y, Chodick G, Shalev V. Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. Rheumatology 2009;48:1107-10.
96. Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis 2010;69:43-7.
97. Tilling L, Townsend S, David J. Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis. Clin Drug Invest 2006;26:55-62.
98. Rosenberg P, Urwitz H, Johannesson A, Ros AM, Lindholm J, Kinnman N, et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. J Hepatol 2007;46:1111-8.
99. Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol 2001;16:1395-401.
100. Di Minno MN, Iervolino S, Peluso R, Russolillo A, Lupoli R, Scarpa R, et al. Hepatic steatosis and disease activity in subjects with psoriatic arthritis receiving tumor necrosis factor-alpha blockers. J Rheumatol 2012;39:1042-6.
101. Bergner R, Peters L, Schmitt V, Loffler C. Leflunomide in dialysis patients with rheumatoid arthritis — A pharmacokinetic study. Clin Rheumatol 2013;32:267-70.
102. Al-Hasani H, Roussou E. Methotrexate for rheumatoid arthritis patients who are on hemodialysis. Rheumatol Int 2011;31:1545-7.
103. Senel S, Kisacik B, Ugan Y, Kasifoglu T, Tunc E, Cobankara V. The efficacy and safety of etanercept in patients with rheumatoid arthritis and spondyloarthropathy on hemodialysis. Clin Rheumatol 2011;30:1369-72.
104. Maza A, Montaudie H, Sbidian E, Gallini A, Aractingi S, Aubin F, et al. Oral cyclosporin in psoriasis: A systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol 2011;25 Suppl 2:19-27.
105. Fine M. Quantifying the impact of NSAID-associated adverse events. Am J Manag Care 2013;19:s267-72.
106. Vassilopoulos D, Calabrese LH. Management of rheumatic disease with comorbid HBV or HCV infection. Nat Rev Rheumatol 2012;8:348-57.