

Infectious, Oncologic, and Autoimmune Comorbidities of Psoriasis and Psoriatic Arthritis: A Report from the GRAPPA 2012 Annual Meeting

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ABSTRACT. At the 2012 annual meeting of the Group for Research and Assessment of Psoriasis and PsA (GRAPPA) in Stockholm, Sweden, members addressed the infectious, oncologic, and autoimmune comorbidities of psoriasis and psoriatic arthritis (PsA). Members discussing infectious comorbidities asked whether patients with psoriasis or PsA are predisposed to particular types of infections, and whether the use of biologic agents is advisable in patients with certain preexisting infections. Regarding the oncologic comorbidities of psoriasis and PsA, members addressed cutaneous malignancy screening, lymphoproliferative malignancy risk and the need for screening, and treatment of patients with preexisting oncologic history requiring systemic therapy. Finally, GRAPPA members discussed autoimmune comorbidities associated with psoriasis and PsA; they agreed that research is nascent in this field and larger studies are necessary to determine the precise magnitude of these associations. (J Rheumatol 2013;40:1438–41; doi:10.3899/jrheum.130458)

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At the 2012 annual meeting of GRAPPA in Stockholm, Sweden, members led discussion groups on the infectious, oncologic, and autoimmune comorbidities of psoriasis and psoriatic arthritis (PsA). Summaries of these discussions are presented here. Cardiovascular comorbidities are addressed in a separate article¹.

Infectious comorbidities of psoriasis and psoriatic arthritis

Discussions of infectious comorbidities of psoriasis and PsA focused on 2 issues: (1) Are patients with psoriasis or PsA predisposed to certain types of infections; and (2) Is the use

of biologic agents advisable in patients with preexisting infections?

The breakout group reviewed the current literature regarding increased infectious risk and expressed a need for further epidemiologic investigations. In a nationally representative survey with laboratory serologic confirmation, patients with psoriasis in the USA do not appear to be at increased risk for hepatitis B (HBV), hepatitis C (HCV), or HIV infection². While some studies suggest possibly increased HCV infection rates in patients with PsA, most have not identified an association between HCV infection and PsA^{3,4,5,6}. In one of the largest case-control studies to date, HCV infection rates in Italy were compared between 100 patients with PsA and 100 controls with rheumatic degenerative disorders⁵. Anti-HCV antibodies were found in 1 (1%) PsA patient and 4 (4%) control patients ($p = 0.68$), suggesting that HCV infection rates were not significantly increased among patients with PsA⁵. It is worth noting, however, that rates of HCV infection, particularly in the older population in Italy, are much higher than in other Western countries⁷.

Risks for developing fungal, bacterial, and serious infections were also discussed. Psoriasis patients may have increased risk for onychomycosis⁸, possibly because their nail dystrophy is a predisposing factor. Compared to patients with atopic dermatitis, patients with psoriasis are at decreased risk for bacterial infection (e.g., *Staphylococcus aureus*), possibly because of their increased expression of host defense genes^{9,10,11}. To date, only 2 studies have

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systematically explored serious infection rates among patients with psoriasis^{12,13}. In a Dutch study, severe psoriasis was associated with increased infection risk requiring hospitalization [hazard ratio (HR) 1.81, 95% CI 1.57–2.08], specifically respiratory tract, abdominal, and skin infections⁹. In a study utilizing a UK database, severe psoriasis was associated with increased infection-related deaths from pneumonia and septicemia (HR 1.65, 95% CI 1.26–2.18)¹⁰.

The group also addressed systemic treatments in patients with psoriasis and PsA with preexisting infectious comorbidities. Treatment selection can be challenging for patients with moderate to severe psoriasis and patients with PsA with concurrent HBV or HCV infection. The group agreed that pretreatment screening for both HBV and HCV should be considered before administering an immunomodulator, although there is no evidence to support routine hepatitis screening at this time¹⁴.

In patients with concurrent HCV infection, the literature shows that tumor necrosis factor (TNF) inhibitors can be used safely in the psoriasis and PsA population, with most studies citing etanercept use^{6,15,16,17,18,19}. In a study of patients with HCV and both psoriasis and PsA who were treated with etanercept for 6 months, their HCV viral load and transaminase levels remained stable¹⁶. Other case reports have corroborated these findings and reported successful treatment of psoriatic diseases with etanercept without exacerbating patients' HCV status^{6,17,18,19}. Therefore, GRAPPA members deemed treatment with anti-TNF therapy acceptable in this population as long as monitoring of patient's liver status is reviewed at appropriate intervals, with monitoring to include aminotransferase levels and, when appropriate, quantitative HCV RNA^{20,21}. It is important that the patient receive coordinated care from both a dermatologist and hepatologist.

In comparison, patients with HBV infection must be approached with great caution due to the significant risk of HBV reactivation with immunosuppressive therapy. HBV reactivation can range from asymptomatic reactions to fulminant hepatitis that is potentially fatal. Isolated cases of HBV reactivation have been reported in patients with psoriasis undergoing TNF inhibitor treatment²². However, other reports suggested that the risk of HBV reactivation in these patients might not be as high as previously thought^{23,24}. Without systematic and sufficiently powered studies, it is difficult to determine the exact rates of HBV reactivation in TNF inhibitor-treated patients. GRAPPA members agreed that in patients with psoriasis with positive HBsAg but inactive HBV disease, it might be prudent to initiate antiviral therapy, in consultation with a hepatologist, several weeks before starting TNF inhibitors. Further, all HBV-seropositive patients receiving anti-TNF therapy need to have regular monitoring of viral load and liver function, with care being coordinated with the treating hepatologist.

Oncologic comorbidities of psoriasis and psoriatic arthritis

Another group discussed oncologic comorbidities of psoriasis and PsA. Because many patients with moderate to severe psoriasis and PsA are treated with systemic immunosuppressive medications, difficulties exist in discerning whether oncologic comorbidities are related to the psoriatic disease process or are modified by the systemic treatments. GRAPPA members agreed that epidemiologic studies dedicated to assessing oncological comorbidities in the PsA population are scarce. One pivotal study directly assessing malignancy rates was performed in 665 patients with PsA from the University of Toronto Psoriatic Arthritis Clinic²⁵. Compared to the general population, these patients with PsA experienced similar types and rates of malignancy. Specifically, the standardized incidence ratio for malignancies was 0.98 (95% CI 0.77–1.24)²⁵, showing that the incidence of malignancy in the PsA cohort did not differ from that in the general population²⁵.

Some epidemiologic studies suggest that patients with psoriasis may be at increased risk for skin cancers and certain lymphoproliferative malignancies^{14,26,27,28,29}, which may be due partly to treatment-related ultraviolet exposure³⁰. Members discussed ways to improve detection of cutaneous malignancies among these patients. First, wearing protective goggles and groin shields during ultraviolet therapy is critical, as patients without protection of the genital skin are at significantly increased risk for developing genital malignancies³¹. Second, full skin examinations at least annually are important for cutaneous malignancy screening. In patients undergoing active ultraviolet treatments or who had undergone a large number of ultraviolet treatments, biannual skin examinations may be considered.

GRAPPA members also examined lymphoproliferative malignancy risks in patients with psoriasis and PsA, noting that most literature in this area concerns malignancy risks among patients treated with biologic agents such as TNF inhibitors. Of the few epidemiologic studies that examined the overall lymphoma risks in the psoriasis population^{27,28}, one used a UK population database, where the investigators found that, compared to the general population, psoriasis patients are at increased risk for lymphoma (HR 1.35, 95% CI 1.17–1.55), and the attributable risk was 7.9/100,000 psoriasis patients/year²⁸. Members discussed whether lymphoproliferative malignancy screen was necessary in these patients. Despite the elevated relative risk for developing lymphoma, members recognized that the absolute risk for developing lymphoma in the psoriasis population was low (IR 3.57/10,000 persons/year, 95% CI 3.14–4.04)²⁸. Overall, members did not find conclusive evidence at this time to support routine lymph node examinations and/or imaging studies in otherwise asymptomatic patients without a history of internal malignancy.

Members also discussed the use of biologic medications

and their effect on tumor development in the psoriasis population. After examining selected studies, including clinical trial data, the members determined that, to date, the literature on the association of TNF inhibitors and solid tumor development do not show significantly increased rates of solid tumors compared to those receiving placebo or to the general populations^{32,33,34,35,36}.

Finally, members discussed how to approach patients with a history of internal malignancy who would otherwise benefit from systemic immunomodulatory agents for their psoriatic disease. In patients with moderate to severe psoriasis with a history of treated solid tumor malignancy or a current solid tumor malignancy, phototherapy with or without acitretin could represent viable treatment considerations. In patients with severe PsA and a history of internal malignancy where TNF inhibitors would be clearly beneficial in reducing joint destruction, the clinicians need to adopt an individualized approach and perform a full benefit-risk analysis. Careful discussions with patients are necessary to ensure they are fully informed of the potential outcomes.

Autoimmune comorbidities of psoriasis and psoriatic arthritis

Autoimmune comorbidities of psoriasis and PsA are under active investigation. Much of the initial interests in autoimmune comorbidities were fueled by genetic studies that found shared loci between psoriasis and certain autoimmune diseases such as Crohn's disease (*IL12B*, *IL4/13* cytokine gene cluster) and rheumatologic diseases (*PTPN22*). GRAPPA members examined the current (though scarce) literature on the relationship between psoriatic diseases and autoimmune diseases. Epidemiologic investigations must be cognizant of the potential pitfalls of "multiple hypothesis testing," where false-positive associations may be identified.

Members discussed the association between psoriasis and celiac disease, an autoimmune disorder of the small intestine where patients develop antibodies to tissue transglutaminase. The majority have either the HLA-DQ2 or HLA-DQ8 isoform. Genome-wide association studies have found an association between celiac disease and a single-nucleotide polymorphism (SNP; rs6822844) located close to loci for *IL2* and *IL21* — the same SNP associated with early-onset psoriasis³⁷. Epidemiologic studies have found higher rates of celiac disease and elevated anti-gliadin antibodies in psoriasis patients compared to the general population^{38,39}. Further, few reports suggest that psoriasis patients with IgA or IgG anti-gliadin antibodies may experience improvement in psoriasis by avoiding gluten^{36,38}. However, larger studies are necessary before recommendations can be made regarding screening anti-gliadin antibodies in psoriasis patients.

Members also discussed the association between

psoriasis and inflammatory bowel disease (IBD). Population studies from Germany, Israel, Switzerland, and the USA have shown that psoriasis is associated with increased prevalence of ulcerative colitis and Crohn's disease (CD)⁴⁰. In general, the magnitude of association is greater with CD (OR 1.6–2.49) than with ulcerative colitis (OR 1.3–1.91)⁴⁰.

There are genetic foundations for the observed epidemiologic associations⁴¹. For example, the susceptibility loci for psoriasis, CD, and ulcerative colitis all appear in *6p21*, which includes *IBD3* that is involved in CD and ulcerative colitis, and *PSORS1* in psoriasis. The non-MHC related genes *IL23R* and *IL12B* are also associated with all 3 diseases.

Population studies have also suggested possible associations between psoriatic diseases and giant cell arteritis and pulmonary fibrosis⁴². To date, however, no strong associations have been identified with other autoimmune diseases such as systemic lupus erythematosus, diabetes mellitus type 1, multiple sclerosis, or Graves' disease⁴⁰.

In summary, GRAPPA members agreed that future studies in comorbidities research must carefully discriminate between comorbidities associated with the psoriatic disease process itself versus those that are associated with and/or modified by the psoriasis and arthritis treatments. Direct assessments of psoriasis and PsA severity will be useful to determine whether a dose-response relationship exists between severity of psoriatic diseases and the severity of the comorbid conditions. While smaller epidemiologic studies can be informative, conclusions from underpowered studies must be carefully interpreted in the context of the study design to avoid interpreting false-negative relationships. Large, sufficiently powered epidemiologic studies are necessary to determine the precise magnitude of the associations.

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