Psoriasis: Which therapy for which patient

Focus on special populations and chronic infections

Shivani B. Kaushik, MD, and Mark G. Lebwohl, MD
New York, New York

Learning objectives
After completing this learning activity, participants should be able to provide a tailored approach for choosing an appropriate treatment regimen for psoriasis patients based on their individual disease characteristics and comorbidities.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
Dr Mark Lebwohl served as an author of this article and has the following financial relationships:

Consultant, Honoraria: Allergan, Inc; Aqua; Arcutis, Inc; Boehringer Ingelheim; Bristol-Myers Squibb; Dr. Reddy; Leo Pharma Inc; Menlo Therapeutics; Mitsibushi Pharma; Neuroderm LTD; Theravance Biopharma; Verrica Pharmaceuticals Inc

Other, Honoraria: Corrona, Inc Foundation for Research & Education of Dermatology

Principal Investigator, Grants/Research Funding: AbbVie; AstraZeneca; Celgene Corporation; Eli Lilly and Company; Incyte Corporation; Janssen Research & Development, LLC; Medimmune; Novartis Pharmaceuticals Corp; Pfizer Inc; SCIderm; UCB; Valeant Pharmaceuticals North America LLC; and Vidac Pharma.

All other authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Despite the availability of several new systemic agents for psoriasis treatment, choosing the right therapy in certain patient populations can be challenging. There are few up-to-date reviews on systemic drugs for moderate to severe psoriasis in pregnant and pediatric patients and in patients with concomitant chronic infections, such as hepatitis, HIV, and latent tuberculosis. These groups are usually excluded from clinical trials, and much of the available evidence is based on anecdotal case reports and case series. As a chronic disease, psoriasis requires long-term treatment, and there are concerns of adverse maternal–fetal outcomes, long-term side effects in children, and the reactivation of latent infections with the use of systemic agents in these patients. The second article in this continuing medical education series provides insights for choosing appropriate systemic agents for treating moderate to severe psoriasis in pregnant and pediatric patients and in the setting of chronic infections, such as hepatitis, HIV, and latent tuberculosis. (J Am Acad Dermatol 2019;80:43-53.)

Keywords: acitretin; adalimumab; apremilast; biologic; brodalumab; certolizumab; cyclosporine; comorbidities; etanercept; golimumab; hepatitis; HIV; IL-12/23; IL-17; IL-23; infliximab; ixekizumab; psoriasis; psoriatic arthritis; methotrexate; pediatric; pregnancy; secukinumab; systemic; TNF-α; traditional agents; tuberculosis; ustekinumab.

From the Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York.
Funding sources: None.
Dr Lebwohl is an employee of Mount Sinai and receives research funds from Abbvie, Boehringer Ingelheim, Eli Lilly, Incyte, Janssen/Johnson & Johnson, Leo Pharmaceuticals, MedImmune/AstraZeneca, Novartis, Pfizer, Sciderm, Valeant, and ViDac. Dr Lebwohl is also a consultant for Allergan, Aqua, Boehringer-Ingelheim, LEO Pharma, Menlo, Mitsubishi, Promius, and Theravance. Dr Kaushik has no conflicts of interest to disclose.

Accepted for publication June 1, 2018.
Reprints not available from the authors.
Correspondence to: Shivani Kaushik, MD, Department of Dermatology, Icahn School of Medicine at Mount Sinai, 1425 Madison Ave, Box 1047, New York, NY 10029. E-mail: docshivanib@gmail.com.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.06.056
Date of release: January 2019
Expiration date: January 2022

Abbreviations used:

FDA:	Food and Drug Administration
HBV:	hepatitis B virus
HCV:	hepatitis C virus
LFT:	liver function test
LTBI:	latent tuberculosis infection
PASI:	Psoriasis Area and Severity Index
TNF:	tumor necrosis factor
VACTERL:	vertebral anomalies, anal atresia cardiac defects, tracheoesophageal fistula and/or esophageal atresia, renal and radial anomalies and limb defects

In addition to the comorbidities discussed in the first article in this continuing medical education series, there are certain other clinical scenarios, such as pregnancy, pediatric age group, and concomitant chronic infections that often complicate the choice of systemic agent for psoriasis. The second article in this continuing medical education series provides insights for choosing an appropriate systemic agent for treating moderate to severe psoriasis in pregnant and pediatric patients and in the setting of chronic infections, hepatitis, HIV, and latent tuberculosis.

PREGNANCY

The treatment of psoriasis in pregnant patients can be challenging. Because of the immunomodulatory changes of pregnancy, psoriasis generally tends to improve, but some patients can experience worsening of psoriasis, warranting the need for systemic treatment.[1] Pregnant patients are excluded from clinical trials and much of the available safety data are obtained from case reports.

Traditional agents

Methotrexate is teratogenic, mutagenic, abortifacient, and is contraindicated in pregnancy. Methotrexate is associated with embryopathy leading to central nervous system, craniofacial, and limb and growth abnormalities.[2] Cyclosporine pregnancy data are mostly obtained from organ transplant patients. Cyclosporine is not a major teratogen, with a prevalence rate for congenital malformations reported to be approximately 3%, similar to that of general population.[3,4] However, there have been reports of low birth weight and preterm deliveries among infants after in utero exposure to cyclosporine.[5-7] Many reports have highlighted the safety of cyclosporine in treating psoriasis in pregnant patients.[8-12]

The teratogenicity of retinoids is the most important concern in women of reproductive potential. Acitretin causes retinoic acid embryopathy, including cardiovascular, ocular, auditory, central nervous system, craniofacial, and skeletal malformations.[13]

Biologics and other newer agents

There is a lack of well controlled studies assessing biologics during pregnancy. Structural differences between different tumor necrosis factor—alpha (TNF-α) inhibitors determines their transplacental transfer and cord blood concentrations. Significant elevation of adalimumab (160%) and infliximab (153%) has been noted in the cord blood of newborns, whereas etanercept levels were only 4% to 7% of that in maternal blood.[14-17] Certolizumab is noted to have low levels in cord blood (3.9%) because it has minimal transplacental transfer because of its pegylated structure. Data from >300 certolizumab-exposed pregnancies show no increase of maternal or fetal adverse events.[18,19] There is concern of a possible association between etanercept and vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula and/or esophageal atresia, renal and radial anomalies, and limb defects (VACTERL) syndrome based on a case report and a review by the US Food and Drug Administration (FDA).[20,21] However, this report had limitations, such as unclear definitions of VACTERL and poor study design, deeming the results uninterpretable.[22] Contrarily, the majority of other studies on etanercept use in pregnancy have been reassuring.[23-26] Also worrisome is a case report of fatal disseminated mycobacterial infection following a routine bacillus Calmette—Guérin vaccination in a neonate born to a mother taking infliximab throughout pregnancy, which raised concern of fetal immunosuppression with in utero exposure to infliximab.[27] A small study of 8 infants exposed to infliximab in utero concluded that infants mounted an appropriate immune response to routine vaccinations and that there were no concerns for immunosuppression.[15] Overall, the incidence rate of adverse outcomes in several reports observed rates similar to the general US population.[28-30] The specific data for adalimumab are limited, but several reports of its use in pregnant women with Crohn's disease and rheumatoid arthritis did not show any evidence of maternal or fetal adverse events.[25,29,31-33] There are no data available for golimumab use in pregnancy. Among the few reports of ustekinumab use in pregnancy, there are 2 reports of delivery of healthy full-term neonates and 1 report of spontaneous abortion.[34-36] There are no reports of apremilast and IL-17 and IL-23 inhibitor use in pregnant women. The animal data on apremilast, secukinumab, and brodalumab use in pregnancy do not demonstrate any embryo-fetal toxicity. Animal studies on ixekizumab showed an increase in neonatal deaths when it was administered from week 20 to birth.[37]

Table I summarizes the pregnancy warnings (previous categories) for the approved systemic agents for psoriasis.

Expert opinion

1. Certolizumab is the most preferred agent because of its minimal transplacental transfer. Etanercept is a good alternative because its placental transfer is less than infliximab and adalimumab
2. Ustekinumab and secukinumab were both FDA pregnancy risk category B when pregnancy categories were assigned and are considered safe, but available data are limited. There are minimal data available on ixekizumab, brodalumab, apremilast, and IL-23 inhibitors
3. Methotrexate and acitretin are absolutely contraindicated in pregnancy. Cyclosporine can be used but its use should be limited to the shortest duration at the lowest possible dose

PEDIATRIC POPULATION

Approximately one third of psoriasis cases develop in childhood, and psoriasis accounts for nearly 4% of all dermatoses seen in children <16 years of age.[39] Among the multiple systemic treatments available for psoriasis in adults, only a few systemic drugs are approved for use in the pediatric population.

Traditional agents

Van Geel et al[40] demonstrated methotrexate therapy to be safe with significant improvement in Psoriasis Area and Severity Index score and quality of life in pediatric psoriasis patients. However, it should be used intermittently to prevent cumulative toxicity.[41-43] Cyclosporine is considered safe in children based on data from its use for other indications, such as atopic dermatitis.[44-46] There are only a few published reports of cyclosporine use in pediatric psoriasis, most of which describe rapid improvement in psoriasis without any major side effects.[47-52]

The major concern with the long-term use of retinoids in children are the skeletal side effects, such as premature closure of epiphysis, calcification of tendons, and hyperostotic changes.[53] In addition, its mucocutaneous side effects can decrease children's compliance to treatment.[41,54] However, acitretin has been used successfully for pediatric pustular, erythrodermic, and severe plaque psoriasis without any significant radiologic abnormalities.[55-61]

Biologics and other newer agents

Etanercept is the only biologic approved for use in children >6 years of age.[62] Adalimumab is approved for the treatment of juvenile idiopathic arthritis in patients ≥4 years of age, and it is currently used off-label for pediatric uveitis, psoriasis, and inflammatory bowel disease.[63] Adalimumab has demonstrated good safety and efficacy in pediatric psoriasis. A phase III trial compared adalimumab and methotrexate in 114 pediatric patients (4-17 years of age) with severe psoriasis. At week 16, a 75% improvement in the Psoriasis Area and Severity Index score in the adalimumab group was 58%, which was significantly higher than 32% in the methotrexate group.[64,65] Infliximab is approved for the treatment of Crohn's disease in children ≥6 years of age.[66] Garber et al[67] reported high clearance rates in pediatric psoriasis with TNF-α blockers (67% with etanercept and adalimumab) and ustekinumab (33%). Data on certolizumab and golimumab use in the pediatric population are limited.

A phase III study (CADMUS) of ustekinumab randomized 110 psoriasis patients who were 12 to 17 years of age to receive placebo or ustekinumab at standard dosing (0.75 mg/kg [≤60 kg], 45 mg [>60-≤100 kg], and 90 mg [>100 kg]) or half standard dosing (0.375 mg/kg [≤60 kg], 22.5 mg [>60-≤100 kg], and 45 mg [>100 kg]). Overall, the standard dose of ustekinumab produced a clinical response in the pediatric population similar to that observed in the adult population and was accompanied by a favorable safety profile.[68] The safety and efficacy of apremilast and IL-17 and IL-23 inhibitors has not been established in the pediatric population as yet, and the related literature is scarce.

Table I. US Food and Drug Administration pregnancy category of systemic agents for psoriasis

Pregnancy category	Systemic agents for psoriasis
B*	Etanercept, adalimumab, infliximab, certolizumab, golimumab, ustekinumab, and secukinumab
C†	Cyclosporine and apremilast
Contraindicated	Methotrexate and acitretin

Recent guidelines by the US Food and Drug Administration abolished the previously used pregnancy categories (A, B, C, D, and X). They have been replaced by narrative summaries providing relevant information to aid health care workers in appropriately prescribing and counseling patients.[38]
*Equivalent to former category B.
†Equivalent to former category C.

Expert opinion

1. Data on TNF-α blockers suggest that these are safe and effective in managing pediatric psoriasis, and etanercept is approved by the US FDA for the treatment of pediatric psoriasis in patients ≥6 years of age
2. Ustekinumab has a convenient dosing schedule for children, making it a preferred agent in

pediatric psoriasis. It is approved for use in adolescents
3. Data on apremilast and IL-17 and IL-23 inhibitors in the pediatric population are limited
4. None of the traditional agents (methotrexate, cyclosporine, and acitretin) are approved by the US FDA for the treatment of pediatric psoriasis, but they are considered safe for intermittent and short-term use

CHRONIC INFECTIONS

Most systemic agents for psoriasis are immunosuppressive, which poses a unique treatment challenge in patients with psoriasis with chronic infections because they are already immunosuppressed. In this section, we discuss treatment strategies for patients with psoriasis who have concomitant hepatitis B virus (HBV) and hepatitis C virus (HCV), HIV, and latent tuberculosis.

Hepatitis

Patients who are eligible for systemic therapy must be screened for the following markers: antibody to hepatitis B core (anti-Hbc Ag), hepatitis B surface antigen (HbsAg), and antibody to HCV (anti-HCV). Based on serology, patients can be categorized into the following groups: 1) HbsAg indicates that person is infectious; 2) anti-Hbc Ag appears with acute infection and persists for life, and immunoglobulin M anti-Hbc indicates acute infection; 3) anti-HbsAg antibody indicates either recovery or immunity because of vaccination; and 4) anti-HCV indicates presumptive or current HCV infection and warrants additional HCV RNA testing.

Traditional agents

Methotrexate is hepatotoxic and has been associated with HBV reactivation.[69-71] A case series reported hepatic fibrosis and cirrhosis in 24% of patients after 5 years of treatment with methotrexate.[72-74] The role of cyclosporine in patients with hepatitis is controversial. There are multiple case reports of HBV and HCV reactivation with cyclosporine in patients who are immunocompromised.[75,76] Cyclosporine is also reportedly associated with the recurrence and progression of HCV leading to severe fibrosis and cirrhosis.[77] Cyclosporine increased the risk of HBV reactivation in patients who were HbsAg-negative/HbcAb-positive transplant patients.[78] Conversely, cyclosporine has demonstrated inhibition of both HBV and HCV in vitro and discontinuation of cyclosporine has been associated with reactivation of the viral infection.[79-82] All systemic therapies for psoriasis except acitretin are immunosuppressive, but acitretin is potentially hepatotoxic.[74] Nonetheless, Roenigk Jr et al[83] reported no significant change in liver histology after 2 years of acitretin use in patients with psoriasis.

Biologics and other newer agents

TNF-α plays an important role in the clearance of hepatitis virus from infected hepatocytes; therefore, TNF-α inhibitors may lead to hepatitis reactivation or disease worsening.[84] There are several reports of hepatitis reactivation in patients who are receiving TNF-α inhibitors.[85-87] Di Nuzzo et al[88] identified 26 publications describing a total of 61 HCV-positive patients who had received anti—TNF-α agents. Most patients did not have any significant change in liver function and HCV viral load. Another study in 15 patients with HCV and psoriatic arthritis showed no significant change in liver enzymes and viral load after anti—TNF-α therapy.[89] There are no reports of golimumab and certolizumab use with HCV infection.

An analysis of 257 HbsAg-positive or anti-Hbc—positive patients receiving anti—TNF-α therapy showed HBV reactivation in 39% of HbsAg-positive patients compared with 5% of anti-Hbc—positive patients. HBV reactivation was more frequent in patients without antiviral prophylaxis compared with patients with antiviral prophylaxis (62% vs 23%; $P = .003$). Patients with anti-Hbc positivity pose a lower risk of viral reactivation compared with patients with HbsAg positivity. If possible, biologics should be avoided in HbsAg-positive patients, but if deemed necessary, patients should receive antiviral prophylaxis before treatment initiation.[85]

In a review of HBV and HCV reactivation in patients with psoriasis who were taking biologics, virus reactivation was noted in 2 of 175 patients who were positive for anti-Hbc antibody, 3 of 97 patients with HCV infection, and 8 of 40 patients with positive HbsAg. The authors concluded that biologics pose minimal risk for viral reactivation in patients with anti-HCV or anti-Hbc antibodies, but they are of considerable risk in HbsAg-positive patients.[90] There are multiple reports of successful etanercept use in patients with psoriasis with coexisting HCV infection.[89,91-98] Zein[99] used etanercept as an adjuvant to interferon and ribavirin for the treatment of HCV infection. The etanercept-treated group noted a higher percentage of patients with HCV-RNA absence and liver fibrosis regression compared with the placebo group. The infliximab package insert warns about rare severe hepatic reactions,

some fatal or necessitating liver transplantation. It also warns about HBV reactivation and recommends monitoring of HBV carriers during and several months after therapy.[100] Frider et al[101] reported a case of drug-induced liver injury caused by adalimumab. Data on certolizumab and golimumab use in hepatitis are limited.

The safety profile of ustekinumab in patients with hepatitis is controversial. Chiu et al[102] assessed the safety of ustekinumab in patients with psoriasis with concurrent HCV and HBV infection. Viral reactivation and hepatocellular cancer were reported in 1 of 4 patients with HCV and in 2 of 7 HbsAg-positive patients who had not received antiviral prophylaxis; reactivation was not noted in 3 HbsAg-negative but anti-Hbc–positive patients. A few other cases of HBV reactivation have been reported with ustekinumab.[103-105] Contrarily, Abuchar et al[106] reported the successful use of ustekinumab for psoriasis without any impact on liver function or viral load in a patient with coexisting HCV. Secukinumab use in hepatitis has been reported in 5 patients with HBV, 3 patients with HCV, and 1 patient with HBV–HCV coinfection. No significant elevation in liver enzymes or virus reactivation was noted in any of these patients.[90,107,108] Data on apremilast use in hepatitis infection are limited. Reddy et al[109] reported a case of concomitant HCV, HIV, and psoriasis treated with apremilast. They did not note any worsening of liver function or viral reactivation.[109] There are no available data on IL-23 inhibitor use in patients with hepatitis.

Expert opinion

Patients should not be treated with immunosuppressive therapies during the acute stage. However, biologic treatment can be initiated in patients with chronic or resolved hepatitis under close monitoring and collaboration with a gastroenterologist.

Anti-HCV–positive

1. TNF-α inhibitors can be used in patients with chronic HCV but with close monitoring of liver function and viral titers, and in conjunction with antiviral therapy
2. The safety profile of ustekinumab is controversial
3. IL-17 inhibitors and apremilast appear to have a favorable safety profile, but the available data are limited. Data are limited on IL-23 inhibitor use in hepatitis
4. Methotrexate is absolutely contraindicated. Acitretin requires monitoring of liver function tests (LFTs). Cyclosporine is controversial, but if used requires monitoring of LFTs and viral titers, and antiviral therapy is prudent

HBV: HbsAg-positive

1. Using TNF-α inhibitors and ustekinumab can lead to viral reactivation, but IL-17 inhibitors appear safe if used after antiviral prophylaxis and with close monitoring of LFTs and viral titers
2. There are no data on apremilast and IL-23 inhibitors
3. Methotrexate and cyclosporine are contraindicated
4. If acitretin is used, monitoring of LFTs is necessary

HBV: Anti-Hbc–positive

1. Lesser risk of HBV reactivation than HbsAg-positive patients; therefore, TNF-α inhibitors, ustekinumab, and IL-17 inhibitors can be used with close monitoring of LFTs and viral titers. There are no data on apremilast and IL-23 inhibitors
2. Methotrexate and cyclosporine are contraindicated
3. If acitretin is used, monitoring of LFTs is necessary

HIV

The prevalence of psoriasis among HIV-positive patients in the United States is reported to be 1% to 3%, which is similar to rates reported in the general population.[110]

Traditional agents

Methotrexate is associated with a high risk of opportunistic infections in patients with HIV. In a case series, 1 patient developed toxic encephalopathy that improved after methotrexate was discontinued.[111] In another study, 4 HIV patients were treated with antiretroviral treatment and received prophylaxis for opportunistic infections before starting methotrexate for psoriasis; 2 of 4 patients developed *Pneumocystis carinii* pneumonia.[112,113]

Data supporting the use of cyclosporine in patients with HIV are limited. There are 2 case reports of successful treatment of psoriasis with cyclosporine in patients with HIV without the development of opportunistic infections or worsening immunosuppression.[114,115] Acitretin is recommended as second-line therapy for moderate to severe psoriasis in patients with HIV because it is a nonimmunosuppressive agent.[116] Buccheri et al[117] treated 11 patients with HIV-associated psoriasis with acitretin monotherapy. Significant clearance was achieved in 36% of patients after 20 weeks of treatment without any deterioration in immune function.[117] Of special note, though not approved for psoriasis,

Table II. Factors to consider when selecting systemic psoriasis treatment

Class of drugs	Drug/special population	Pregnancy	Pediatric	Anti-HCVAb+	HbsAg+	Anti-Hbc+	HIV	Latent TB
TNF-α inhibitors	Etanercept	+	++	++*	–	+/-*	+*	–
	Adalimumab	+	++	+*	–	+/-*	+*	–
	Infliximab	+	+	+*	–	+/-*	+*	–
	Certolizumab	++	+	+*	–	+/-*	+*	–
	Golimumab	+	++	+*	–	+/-*	+*	–
IL-12/23 inhibitor	Ustekinumab	+	++	–	–	?/+*	+*	–
IL-17 inhibitors								
Anti–IL-17A	Secukinumab	?/+	?/+	?/+*	?/+*	?/+*	?/+*	+
Anti–IL-17A	Ixekizumab	?/+	?/+	?/+*	?/+*	?/+*	?/+*	+
Anti–IL-17 receptor	Brodalumab	?/+	?/+	?/+*	?/+*	?/+*	?/+*	+
IL-23 inhibitors	Guselkumab	?	?/+	?	?	?	?	?
	Tildrakizumab	?	?/+	?	?	?	?	?
	Risankizumab	?	?/+	?	?	?	?	?
	Mirikizumab	?	?/+	?	?	?	?	?
Oral novel	Apremilast	?	?/+	?/+*	?	?	+*	+
Oral traditional	Methotrexate	x	+	X	x	x	x	x
	Cyclosporine	+	+	+/–*	x	x	x	x
	Acitretin	x	+	+	+	+	+	+

Note: Two plus symbols (++) indicates preferred agents; one plus symbol (+) indicates that the agent can be used; one plus symbol and one minus symbol (+/–) indicate that the drug can be used but is controversial; one minus symbol and one plus symbol (–/+) indicates that the drug is not preferred but can be used; one question mark and one plus symbol (?/+) indicates that there are not enough data but that the drug is likely safe to use; one question mark (?) indicates that there are not enough data; one minus symbol (–) indicates that use of that drug is controversial because there are not enough data; and x indicates that a drug is contraindicated.
Anti-Hbc, Antibody to hepatitis B core; *anti-HCV*, antibody to hepatitis C virus; *HbsAg*, hepatitis B surface antigen; *TB*, tuberculosis.
*Additional monitoring required.

hydroxyurea has been recommended in patients with psoriasis and HIV infection because of its antiretroviral properties and historic use for psoriasis.[118]

Biologics and other newer agents

There are a few reports of successful etanercept use in patients with HIV with psoriasis, with only 1 report of polymicrobial infection; CD4 and viral counts either improved or remained stable after treatment.[119-123] Infliximab has also been used successfully in patients with HIV and psoriasis. Cepeda et al[124] reported 8 patients with HIV with various rheumatologic diseases that were treated with etanercept or infliximab. During therapy, CD4 counts remained stable and no opportunistic infections were reported.[124-126] There is 1 case report of successful treatment of HIV-associated psoriasis with adalimumab with significant improvement in his CD4 count and viral load.[127] There are no reports on the use of certolizumab and golimumab in HIV-positive patients. Ustekinumab has also been used successfully in patients with HIV on antiretroviral treatment with improvement in CD4 and viral counts.[128,129] Apremilast use has been reported in a patient with concomitant HIV and HCV without any adverse events.[109] There are no data on the use of IL-17 and IL-23 inhibitors in HIV-associated psoriasis.

Expert opinion

1. TNF-α inhibitors, ustekinumab, and apremilast can be used to treat psoriasis in HIV, but these patients should be managed in collaboration with infectious disease specialists for close monitoring of CD4 count and viral load
2. There are no data on IL-17 and Il-23 inhibitor use in patients with HIV, but they are less commonly complicated by opportunistic infections than TNF-α inhibitors
3. Acitretin can be used in patients with HIV, but methotrexate and cyclosporine should be avoided because of the risk of opportunistic infections

LATENT TUBERCULOSIS

Approximately 4.2% of the US population is affected by latent tuberculosis infection (LTBI).[130,131] All patients should be screened for LTBI with either a tuberculin skin test or interferon gamma release assay (IGRA) before starting any immunosuppressive systemic therapy.[132] A positive screening test requires further medical evaluation and a chest radiograph.

Normal chest radiography suggests LTBI, and these patients should receive isoniazid prophylaxis for 1 to 2 months before biologic initiation can also be considered acceptable.[132,133]

Traditional agents

There is a well-recognized association between methotrexate-induced immunosuppression and LTBI reactivation. Several cases of pulmonary and extrapulmonary tuberculosis have been reported in patients with rheumatoid arthritis and psoriasis on methotrexate therapy.[134-136]

Higher doses of cyclosporine have been associated with LTBI reactivation in solid organ transplant patients, but no cases have been reported in patients with psoriasis, likely because of relatively lower doses used in the dermatologic setting.[137-139] There are no reports of LTBI reactivation with acitretin.

Biologics and other newer agents

TNF-α is essential for granuloma formation and plays an important role in host defense against intracellular pathogens like mycobacteria. Multiple cases of tuberculosis infection have been described with all TNF-α blockers.[140,141] The FDA adverse event reporting system reported tuberculosis infection in 144 of 100,000 patients receiving infliximab and in 35 of 100,000 patients receiving etanercept. Among the TNF-α blockers, infliximab is the most frequently associated agent with LTBI reactivation, likely because of the greater and prolonged TNF blockade.[142] Certolizumab and golimumab have also led to LTBI reactivation, specifically in patients who did not receive isoniazid prophylaxis.[143,144] Phase III trials of ustekinumab identified 167 patients with LTBI before treatment initiation; only 1 patient who had not received INH prophylaxis experienced LTBI reactivation. Another case of LTBI reactivation has been reported with ustekinumab even though the patient received isoniazid prophylaxis.[145] So far, no cases of LTBI reactivation have been reported with apremilast or IL-17 and IL-23 blockers.

Expert opinion

1. It is safe to use IL-17 inhibitors and apremilast in patients with LTBI
2. TNF-α inhibitors and ustekinumab can be used only after tuberculosis prophylaxis has been initiated for at least a month
3. Additional safety data are needed for IL-23 inhibitors
4. Methotrexate and cyclosporine can be used in patients with LTBI after tuberculosis prophylaxis
5. Acitretin is safe to use in this setting

In conclusion, the decision to use systemic agents to treat psoriasis in pregnant and pediatric populations requires careful analysis of the risks and benefits to maternal–fetal health and long-term safety in children. In addition, most systemic agents used in psoriasis are immunosuppressive and require appropriate screening, monitoring, and prophylaxis when used in patients with chronic infections, such as hepatitis, HIV, and LTBI. A summary of our expert opinion is shown in Table II. Up-to-date literature on the use of systemic agents in these settings is scarce, and more long-term studies and safety data are warranted.

REFERENCES

1. Weatherhead S, Robson SC, Reynolds NJ. Management of psoriasis in pregnancy. *BMJ*. 2007;334:1218-1220.
2. Feldkamp M, Carey JC. Clinical teratology counseling and consultation case report: low dose methotrexate exposure in the early weeks of pregnancy. *Teratology*. 1993;47:533-539.
3. Bar Oz B, Hackman R, Einarson T, Koren G. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. *Transplantation*. 2001;71:1051-1055.
4. Lamarque V, Leleu MF, Monka C, Krupp P. Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun. *Transpl Proc*. 1997;29:2480.
5. Armenti VT, Ahlswede KM, Ahlswede BA, et al. Variables affecting birthweight and graft survival in 197 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation*. 1995;59:476-479.
6. Sgro MD, Barozzino T, Mirghani HM, et al. Pregnancy outcome post renal transplantation. *Teratology*. 2002;65:5-9.
7. Miniero R, Tardivo I, Curtoni ES, et al. Outcome of pregnancy after organ transplantation: a retrospective survey in Italy. *Transpl Int*. 2005;17:724-729.
8. Wright S, Glover M, Baker H. Psoriasis, cyclosporine, and pregnancy. *Arch Dermatol*. 1991;127:426.
9. Kapoor R, Kapoor JR. Cyclosporine resolves generalized pustular psoriasis of pregnancy. *Arch Dermatol*. 2006;142:1373-1375.
10. Edmonds EV, Morris SD, Short K, Bewley SJ, Eady RA. Pustular psoriasis of pregnancy treated with ciclosporin and high-dose prednisolone. *Clin Exp Dermatol*. 2005;30:709-710.
11. Finch TM, Tan CY. Pustular psoriasis exacerbated by pregnancy and controlled by cyclosporin A. *Br J Dermatol*. 2000;142:582-584.
12. Raddadi AA, Baker Damanhoury Z. Cyclosporin and pregnancy. *Br J Dermatol*. 1999;140:1197-1198.
13. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. 2009;61:451-485.
14. Zelinkova Z, de Haar C, de Ridder L, et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther*. 2011;33:1053-1058.
15. Mahadevan U, Cucchiara S, Hyams JS, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. *Am J Gastroenterol*. 2011;106:214-223.

16. Vasiliauskas EA, Church JA, Silverman N, Barry M, Targan SR, Dubinsky MC. Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. *Clin Gastroenterol Hepatol*. 2006;4:1255-1258.
17. Berthelsen BG, Fjeldsoe-Nielsen H, Nielsen CT, Hellmuth E. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. *Rheumatology (Oxford)*. 2010;49:2225-2227.
18. Forger F, Zbinden A, Villiger PM. Certolizumab treatment during late pregnancy in patients with rheumatic diseases: low drug levels in cord blood but possible risk for maternal infections. A case series of 13 patients. *Joint Bone Spine*. 2016; 83:341-343.
19. Clowse ME, Wolf DC, Forger F, et al. Pregnancy outcomes in subjects exposed to certolizumab pegol. *J Rheumatol*. 2015; 42:2270-2278.
20. Carter JD, Valeriano J, Vasey FB. Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. *J Rheumatol*. 2006;33:1014-1017.
21. Carter JD, Ladhani A, Ricca LR, Valeriano J, Vasey FB. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. *J Rheumatol*. 2009;36:635-641.
22. Winger EE, Reed JL. Was risk properly assessed in Carter, et al's safety assessment of tumor necrosis factor antagonists during pregnancy? *J Rheumatol*. 2009;36:2122.
23. Rump JA, Schonborn H. Conception and course of eight pregnancies in five women on TNF blocker etanercept treatment [in German]. *Z Rheumatol*. 2010;69:903-909.
24. Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, Ornoy A. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. *Reprod Toxicol*. 2014;43:78-84.
25. Berthelot JM, De Bandt M, Goupille P, et al. Exposition to anti-TNF drugs during pregnancy: outcome of 15 cases and review of the literature. *Joint Bone Spine*. 2009;76:28-34.
26. Natsumi I, Matsukawa Y, Miyagawa K, et al. Successful childbearing in two women with rheumatoid arthritis and a history of miscarriage after etanercept treatment. *Rheumatol Int*. 2013;33:2433-2435.
27. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis*. 2010;4:603-605.
28. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol*. 2006;4:621-630.
29. Vesga L, Terdiman JP, Mahadevan U. Adalimumab use in pregnancy. *Gut*. 2005;54:890.
30. Schnitzler F, Fidder H, Ferrante M, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis*. 2011;17:1846-1854.
31. Mishkin DS, Van Deinse W, Becker JM, Farraye FA. Successful use of adalimumab (Humira) for Crohn's disease in pregnancy. *Inflamm Bowel Dis*. 2006;12:827-828.
32. Coburn LA, Wise PE, Schwartz DA. The successful use of adalimumab to treat active Crohn's disease of an ileoanal pouch during pregnancy. *Dig Dis Sci*. 2006;51: 2045-2047.
33. Hyrich KL, Symmons DP, Watson KD, Silman AJ. Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. *Arthritis Rheum*. 2006;54:2701-2702.
34. Andrulonis R, Ferris LK. Treatment of severe psoriasis with ustekinumab during pregnancy. *J Drugs Dermatol*. 2012;11: 1240.
35. Alsenaid A, Prinz JC. Inadvertent pregnancy during ustekinumab therapy in a patient with plaque psoriasis and impetigo herpetiformis. *J Eur Acad Dermatol Venereol*. 2016; 30:488-490.
36. Fotiadou C, Lazaridou E, Sotiriou E, Ioannides D. Spontaneous abortion during ustekinumab therapy. *J Dermatol Case Rep*. 2012;6:105-107.
37. Clarke DO, Hilbish KG, Waters DG, Newcomb DL, Chellman GJ. Assessment of ixekizumab, an interleukin-17A monoclonal antibody, for potential effects on reproduction and development, including immune system function, in cynomolgus monkeys. *Reprod Toxicol*. 2015;58:160-173.
38. Danesh MJ, Murase JE. The new US Food and Drug Administration pregnancy and lactation labeling rules: their impact on clinical practice. *J Am Acad Dermatol*. 2015;73: 310-311.
39. Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. *Pediatr Dermatol*. 2000;17:174-178.
40. van Geel MJ, Oostveen AM, Hoppenreijs EP, et al. Methotrexate in pediatric plaque-type psoriasis: Long-term daily clinical practice results from the Child-CAPTURE registry. *J Dermatolog Treat*. 2015;26:406-412.
41. Kaur I, Dogra S, De D, Kanwar AJ. Systemic methotrexate treatment in childhood psoriasis: further experience in 24 children from India. *Pediatr Dermatol*. 2008;25:184-188.
42. Kumar B, Dhar S, Handa S, Kaur I. Methotrexate in childhood psoriasis. *Pediatr Dermatol*. 1994;11:271-273.
43. Dogra S, Kumaran MS, Handa S, Kanwar AJ. Methotrexate for generalized pustular psoriasis in a 2-year-old child. *Pediatr Dermatol*. 2005;22:85-86.
44. Berth-Jones J, Finlay AY, Zaki I, et al. Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *J Am Acad Dermatol*. 1996;34:1016-1021.
45. Harper JI, Ahmed I, Barclay G, et al. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol*. 2000;142:52-58.
46. Harper JI, Berth-Jones J, Camp RD, et al. Cyclosporin for atopic dermatitis in children. *Dermatology*. 2001;203:3-6.
47. Kilic SS, Hacimustafaoglu M, Celebi S, Karadeniz A, Ildirim I. Low dose cyclosporin A treatment in generalized pustular psoriasis. *Pediatr Dermatol*. 2001;18:246-248.
48. Alli N, Gungor E, Karakayali G, Lenk N, Artuz F. The use of cyclosporin in a child with generalized pustular psoriasis. *Br J Dermatol*. 1998;139:754-755.
49. Torchia D, Terranova M, Fabbri P. Photosensitive psoriasis in a vitiligo patient. *J Dermatol*. 2006;33:880-883.
50. Wollina U, Funfstuck V. Juvenile generalized circinate pustular psoriasis treated with oral cyclosporin A. *Eur J Dermatol*. 2001;11:117-119.
51. Kim HS, Kim GM, Kim SY. Two-stage therapy for childhood generalized pustular psoriasis: low-dose cyclosporin for induction and maintenance with acitretin/narrowband ultraviolet B phototherapy. *Pediatr Dermatol*. 2006;23:306-308.
52. Pereira TM, Vieira AP, Fernandes JC, Sousa-Basto A. Cyclosporin A treatment in severe childhood psoriasis. *J Eur Acad Dermatol Venereol*. 2006;20:651-656.
53. Perrett CM, Ilchyshyn A, Berth-Jones J. Cyclosporin in childhood psoriasis. *J Dermatolog Treat*. 2003;14:113-118.
54. Ruiz-Maldonado R, Tamayo L. Retinoids in disorders of keratinization: their use in children. *Dermatologica*. 1987; 175(suppl 1):125-132.

55. Lee CS, Koo J. A review of acitretin, a systemic retinoid for the treatment of psoriasis. *Expert Opin Pharmacother*. 2005;6:1725-1734.
56. Kopp T, Karlhofer F, Szepfalusi Z, Schneeberger A, Stingl G, Tanew A. Successful use of acitretin in conjunction with narrowband ultraviolet B phototherapy in a child with severe pustular psoriasis, von Zumbusch type. *Br J Dermatol*. 2004;151:912-916.
57. de Oliveira ST, Maragno L, Arnone M, Fonseca Takahashi MD, Romiti R. Generalized pustular psoriasis in childhood. *Pediatr Dermatol*. 2010;27:349-354.
58. Juanqin G, Zhiqiang C, Zijia H. Evaluation of the effectiveness of childhood generalized pustular psoriasis treatment in 30 cases. *Pediatr Dermatol*. 1998;15:144-146.
59. Chao PH, Cheng YW, Chung MY. Generalized pustular psoriasis in a 6-week-old infant. *Pediatr Dermatol*. 2009;26:352-354.
60. Salleras M, Sanchez-Regana M, Umbert P. Congenital erythrodermic psoriasis: case report and literature review. *Pediatr Dermatol*. 1995;12:231-234.
61. Ergin S, Ersoy-Evans S, Sahin S, Ozkaya O. Acitretin is a safe treatment option for infantile pustular psoriasis. *J Dermatolog Treat*. 2008;19:341-343.
62. Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med*. 2008;358:241-251.
63. Fortina AB, Bardazzi F, Berti S, et al. Treatment of severe psoriasis in children: recommendations of an Italian expert group. *Eur J Pediatr*. 2017;176:1339-1354.
64. Marqueling AL, Cordoro KM. Systemic treatments for severe pediatric psoriasis: a practical approach. *Dermatol Clin*. 2013;31:267-288.
65. Papp K, Thaci D, Marcoux D, et al. Efficacy and safety of adalimumab every other week versus methotrexate once weekly in children and adolescents with severe chronic plaque psoriasis: a randomised, double-blind, phase 3 trial. *Lancet*. 2017;390:40-49.
66. Baldassano RN. Infliximab in pediatric Crohn's disease patients. *Gastroenterol Hepatol (N Y)*. 2006;2:467.
67. Garber C, Creighton-Smith M, Sorensen EP, Dumont N, Gottlieb AB. Systemic treatment of recalcitrant pediatric psoriasis: a case series and literature review. *J Drugs Dermatol*. 2015;14:881-886.
68. Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. *J Am Acad Dermatol*. 2015;73:594-603.
69. Cobeta Garcia JC, Medrano M. Reactivation of hepatitis B in a patient with spondyloarthritis after the suspension of methotrexate and efficacy of treatment with antivirals in association to adalimumab [in Spanish]. *Reumatol Clin*. 2011;7:200-202.
70. Hagiyama H, Kubota T, Komano Y, Kurosaki M, Watanabe M, Miyasaka N. Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis. *Clin Exp Rheumatol*. 2004;22:375-376.
71. Gwak GY, Koh KC, Kim HY. Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. *Clin Exp Rheumatol*. 2007;25:888-889.
72. Ashton RE, Millward-Sadler GH, White JE. Complications in methotrexate treatment of psoriasis with particular reference to liver fibrosis. *J Invest Dermatol*. 1982;79:229-232.
73. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. *Arch Dermatol*. 2012;148:95-102.
74. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2015;29:2277-2294.
75. Sandrini S, Callea F, Cristinelli L, et al. Viral hepatitis in HBsAg-positive renal transplant patients treated with cyclosporin and steroids. *Nephrol Dial Transpl*. 1990;5:525-530.
76. Dai MS, Kao WY, Shyu RY, Chao TY. Restoration of immunity and reactivation of hepatitis B virus after immunosuppressive therapy in a patient with severe aplastic anaemia. *J Viral Hepat*. 2004;11:283-285.
77. Papatheodoridis GV, Davies S, Dhillon AP, et al. The role of different immunosuppression in the long-term histological outcome of HCV reinfection after liver transplantation for HCV cirrhosis. *Transplantation*. 2001;72:412-418.
78. Mikulska M, Nicolini L, Signori A, et al. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. *Clin Microbiol Infect*. 2014;20:O694-O701.
79. Xia WL, Shen Y, Zheng SS. Inhibitory effect of cyclosporine A on hepatitis B virus replication in vitro and its possible mechanisms. *Hepatobiliary Pancreat Dis Int*. 2005;4:18-22.
80. Watashi K, Hijikata M, Hosaka M, Yamaji M, Shimotohno K. Cyclosporin A suppresses replication of hepatitis C virus genome in cultured hepatocytes. *Hepatology*. 2003;38:1282-1288.
81. Yoshiba M, Sekiyama K, Sugata F, Kanamori H, Kodama F, Okamoto H. Activation of hepatitis C virus following immunosuppressive treatment. *Dig Dis Sci*. 1992;37:478.
82. Gruber A, Lundberg LG, Bjorkholm M. Reactivation of chronic hepatitis C after withdrawal of immunosuppressive therapy. *J Intern Med*. 1993;234:223-225.
83. Roenigk HH Jr, Callen JP, Guzzo CA, et al. Effects of acitretin on the liver. *J Am Acad Dermatol*. 1999;41:584-588.
84. Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. *Ann Rheum Dis*. 2006;65:983-989.
85. Perez-Alvarez R, Diaz-Lagares C, Garcia-Hernandez F, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine (Baltimore)*. 2011;90:359-371.
86. Sansone S, Guarino M, Castiglione F, et al. Hepatitis B and C virus reactivation in immunosuppressed patients with inflammatory bowel disease. *World J Gastroenterol*. 2014;20:3516-3524.
87. Vigano M, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: safety and clinical management. *Expert Opin Biol Ther*. 2012;12:193-207.
88. Di Nuzzo S, Boccaletti V, Fantini C, et al. Are anti-TNF-alpha agents safe for treating psoriasis in hepatitis C virus patients with advanced liver disease? Case reports and review of the literature. *Dermatology*. 2016;232:102-106.
89. Costa L, Caso F, Atteno M, et al. Long-term safety of anti-TNF-alpha in PsA patients with concomitant HCV infection: a retrospective observational multicenter study on 15 patients. *Clin Rheumatol*. 2014;33:273-276.
90. Snast I, Atzmony L, Braun M, Hodak E, Pavlovsky L. Risk for hepatitis B and C virus reactivation in patients with psoriasis on biologic therapies: a retrospective cohort study and

systematic review of the literature. *J Am Acad Dermatol*. 2017;77:88-97.e5.
91. Magliocco MA, Gottlieb AB. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. *J Am Acad Dermatol*. 2004;51:580-584.
92. Rokhsar C, Rabhan N, Cohen SR. Etanercept monotherapy for a patient with psoriasis, psoriatic arthritis, and concomitant hepatitis C infection. *J Am Acad Dermatol*. 2006;54:361-362.
93. De Simone C, Paradisi A, Capizzi R, Carbone A, Siciliano M, Amerio PL. Etanercept therapy in two patients with psoriasis and concomitant hepatitis C. *J Am Acad Dermatol*. 2006;54:1102-1104.
94. Prignano F, Ricceri F, Pescitelli L, Zanieri F, Lotti T. Tumour necrosis factor-alpha antagonists in patients with concurrent psoriasis and hepatitis B or hepatitis C: a retrospective analysis of 17 patients. *Br J Dermatol*. 2011;164:645-647.
95. Navarro R, Vilarrasa E, Herranz P, et al. Safety and effectiveness of ustekinumab and antitumour necrosis factor therapy in patients with psoriasis and chronic viral hepatitis B or C: a retrospective, multicentre study in a clinical setting. *Br J Dermatol*. 2013;168:609-616.
96. Khanna M, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. *J Dermatolog Treat*. 2003;14:229-232.
97. Cecchi R, Bartoli L. Psoriasis and hepatitis C treated with anti-TNF alpha therapy (etanercept). *Dermatol Online J*. 2006;12:4.
98. Pritchard C. Etanercept and hepatitis C. *J Clin Rheumatol*. 1999;5:179.
99. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol*. 2005;42:315-322.
100. Brunasso AM, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. *Rheumatology (Oxford)*. 2011;50:1700-1711.
101. Frider B, Bruno A, Ponte M, Amante M. Drug-induced liver injury caused by adalimumab: a case report and review of the bibliography. *Case Rep Hepatol*. 2013;2013:406901.
102. Chiu HY, Chen CH, Wu MS, Cheng YP, Tsai TF. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. *Br J Dermatol*. 2013;169:1295-1303.
103. Purnak S, Purnak T. Hepatitis B virus reactivation after ustekinumab treatment. *Br J Dermatol*. 2014;170:477-478.
104. Koskinas J, Tampaki M, Doumba PP, Rallis E. Hepatitis B virus reactivation during therapy with ustekinumab for psoriasis in a hepatitis B surface-antigen-negative anti-HBs-positive patient. *Br J Dermatol*. 2013;168:679-680.
105. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371:1665-1674.
106. Abuchar A, Vitiello M, Kerdel FA. Psoriasis treated with ustekinumab in a patient with hepatitis C. *Int J Dermatol*. 2013;52:381-382.
107. Bevans SL, Mayo TT, Elewski BE. Safety of secukinumab in hepatitis B virus. *J Eur Acad Dermatol Venereol*. 2018;32:e120-e121.
108. Yanagihara S, Sugita K, Yoshida Y, Tsuruta D, Yamamoto O. Psoriasis vulgaris in a hepatitis B virus carrier successfully treated with secukinumab and entecavir combination therapy. *Eur J Dermatol*. 2017;27:185-186.
109. Reddy SP, Shah VV, Wu JJ. Apremilast for a psoriasis patient with HIV and hepatitis C. *J Eur Acad Dermatol Venereol*. 2017;31:e481-e482.
110. Mallon E, Bunker CB. HIV-associated psoriasis. *AIDS Patient Care STDS*. 2000;14:239-246.
111. Duvic M, Johnson TM, Rapini RP, Freese T, Brewton G, Rios A. Acquired immunodeficiency syndrome-associated psoriasis and Reiter's syndrome. *Arch Dermatol*. 1987;123:1622-1632.
112. Masson C, Chennebault JM, Leclech C. Is HIV infection contraindication to the use of methotrexate in psoriatic arthritis? *J Rheumatol*. 1995;22:2191.
113. Maurer TA, Zackheim HS, Tuffanelli L, Berger TG. The use of methotrexate for treatment of psoriasis in patients with HIV infection. *J Am Acad Dermatol*. 1994;31(2 pt 2):372-375.
114. Tourne L, Durez P, Van Vooren JP, et al. Alleviation of HIV-associated psoriasis and psoriatic arthritis with cyclosporine. *J Am Acad Dermatol*. 1997;37(3 pt 1):501-502.
115. Allen BR. Use of cyclosporin for psoriasis in HIV-positive patient. *Lancet*. 1992;339:686.
116. Menon K, Van Voorhees AS, Bebo BF Jr, et al. Psoriasis in patients with HIV infection: from the medical board of the National Psoriasis Foundation. *J Am Acad Dermatol*. 2010;62:291-299.
117. Buccheri L, Katchen BR, Karter AJ, Cohen SR. Acitretin therapy is effective for psoriasis associated with human immunodeficiency virus infection. *Arch Dermatol*. 1997;133:711-715.
118. Lee ES, Heller MM, Kamangar F, Park K, Liao W, Koo J. Hydroxyurea for the treatment of psoriasis including in HIV-infected individuals: a review. *Psoriasis Forum*. 2011;17:180-187.
119. Di Lernia V, Zoboli G, Ficarelli E. Long-term management of HIV/hepatitis C virus associated psoriasis with etanercept. *Indian J Dermatol Venereol Leprol*. 2013;79:444.
120. Lee ES, Heller MM, Kamangar F, Park KK, Koo JY. Long-term etanercept use for severe generalized psoriasis in an HIV-infected individual: a case study. *J Drugs Dermatol*. 2012;11:413-414.
121. Mikhail M, Weinberg JM, Smith BL. Successful treatment with etanercept of von Zumbusch pustular psoriasis in a patient with human immunodeficiency virus. *Arch Dermatol*. 2008;144:453-456.
122. Linardaki G, Katsarou O, Ioannidou P, Karafoulidou A, Boki K. Effective etanercept treatment for psoriatic arthritis complicating concomitant human immunodeficiency virus and hepatitis C virus infection. *J Rheumatol*. 2007;34:1353-1355.
123. Aboulafia DM, Bundow D, Wilske K, Ochs UI. Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. *Mayo Clin Proc*. 2000;75:1093-1098.
124. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. *Ann Rheum Dis*. 2008;67:710-712.
125. Sellam J, Bouvard B, Masson C, et al. Use of infliximab to treat psoriatic arthritis in HIV-positive patients. *Joint Bone Spine*. 2007;74:197-200.
126. Bartke U, Venten I, Kreuter A, Gubbay S, Altmeyer P, Brockmeyer NH. Human immunodeficiency virus-associated psoriasis and psoriatic arthritis treated with infliximab. *Br J Dermatol*. 2004;150:784-786.
127. Lindsey SF, Weiss J, Lee ES, Romanelli P. Treatment of severe psoriasis and psoriatic arthritis with adalimumab in an HIV-positive patient. *J Drugs Dermatol*. 2014;13:869-871.

128. Saeki H, Ito T, Hayashi M, et al. Successful treatment of ustekinumab in a severe psoriasis patient with human immunodeficiency virus infection. *J Eur Acad Dermatol Venereol*. 2015;29:1653-1655.
129. Paparizos V, Rallis E, Kirsten L, Kyriakis K. Ustekinumab for the treatment of HIV psoriasis. *J Dermatolog Treat*. 2012;23:398-399.
130. Bennett DE, Courval JM, Onorato I, et al. Prevalence of tuberculosis infection in the United States population: the national health and nutrition examination survey, 1999-2000. *Am J Respir Crit Care Med*. 2008;177:348-355.
131. Horsburgh CR Jr, Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. *N Engl J Med*. 2011;364:1441-1448.
132. Doherty SD, Van Voorhees A, Lebwohl MG, et al. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. *J Am Acad Dermatol*. 2008;59:209-217.
133. Amerio P, Amoruso G, Bardazzi F, et al. Detection and management of latent tuberculosis infections before biologic therapy for psoriasis. *J Dermatolog Treat*. 2013;24:305-311.
134. di Girolamo C, Pappone N, Melillo E, Rengo C, Giuliano F, Melillo G. Cavitary lung tuberculosis in a rheumatoid arthritis patient treated with low-dose methotrexate and steroid pulse therapy. *Br J Rheumatol*. 1998;37:1136-1137.
135. Binymin K, Cooper RG. Late reactivation of spinal tuberculosis by low-dose methotrexate therapy in a patient with rheumatoid arthritis. *Rheumatology (Oxford)*. 2001;40:341-342.
136. Smith JD, Knox JM. Psoriasis, methotrexate and tuberculosis. *Br J Dermatol*. 1971;84:590-593.
137. Sundaram M, Adhikary SD, John GT, Kekre NS. Tuberculosis in renal transplant recipients. *Indian J Urol*. 2008;24:396-400.
138. John GT, Shankar V. Mycobacterial infections in organ transplant recipients. *Semin Respir Infect*. 2002;17:274-283.
139. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. European FK506 Multicentre Liver Study Group. *Lancet*. 1994;344:423-428.
140. Desai SB, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. *Best Pract Res Clin Rheumatol*. 2006;20:757-790.
141. Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum*. 2007;57:756-761.
142. Culver EL, Travis SP. How to manage the infectious risk under anti-TNF in inflammatory bowel disease. *Curr Drug Targets*. 2010;11:198-218.
143. Mariette X, Vencovsky J, Lortholary O, et al. The incidence of tuberculosis in patients treated with certolizumab pegol across indications: impact of baseline skin test results, more stringent screening criteria and geographic region. *RMD Open*. 2015;1:e000044.
144. Kay J, Fleischmann R, Keystone E, et al. Five-year safety data from 5 clinical trials of subcutaneous golimumab in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol*. 2016;43:2120-2130.
145. Tsai TF, Ho V, Song M, et al. The safety of ustekinumab treatment in patients with moderate-to-severe psoriasis and latent tuberculosis infection. *Br J Dermatol*. 2012;167:1145-1152.

Answers to CME examination

Identification No. JD0119

January 2019 issue of the Journal of the American Academy of Dermatology.

Kaushik SB, Lebwohl MG. J Am Acad Dermatol 2019;80:43-53.

1.b
2.d