Practical Strategies for Optimizing Management of Psoriasis

Jashin J. Wu, MD,* April W. Armstrong, MD, MPH,† Kenneth B. Gordon, MD,‡ and M. Alan Menter, MD§

Abstract

Approximately 30% of patients with moderate plaque psoriasis and 20% of those with severe psoriasis have inadequate disease control with their current therapeutic regimens. Among the factors that affect treatment efficacy are drug selection and lack of patient adherence to treatment, which is often due to patient frustration that psoriasis is a chronic, multisystemic, and incurable disease. By forming a strong therapeutic alliance with patients and by asking them about their expectations for treatment, clinicians have a better chance of providing patients with more effective and durable relief from their psoriasis symptoms.

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Keywords

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*Director of Dermatology Research, Department of Dermatology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California
† Associate Professor of Clinical Dermatology, Associate Dean for Clinical Research, Keck School of Medicine of the University of Southern California, Los Angeles, California
‡ Professor and Chair, Department of Dermatology, Medical College of Wisconsin, Milwaukee, Wisconsin
§ Chairman, Division of Dermatology, Baylor University Medical Center, Dallas, Texas

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Jashin J. Wu, MD, *Contracted Research:* AbbVie Inc., Amgen Inc., Eli Lilly and Company, Janssen Biotech, Inc., Novartis Pharmaceuticals Corporation, Regeneron.

April W. Armstrong, MD, MPH, *Consultant:* AbbVie Inc., Amgen Inc., Eli Lilly and Company, Janssen Biotech, Inc., Modernizing Medicine, Novartis Pharmaceuticals Corporation, Regeneron, Sanofi. *Speakers Bureau:* AbbVie Inc., Eli Lilly and Company, Janssen Biotech, Inc.

Kenneth B. Gordon, MD, *Consultant:* AbbVie Inc., Amgen Inc., Almirall, S.A., Boehringer Ingelheim, Bristol Myers-Squibb Company, Celgene Corporation, Dermira, Inc., Eli Lilly and Company, LEO Pharma Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Sun Pharmaceutical Industries Ltd., UCB, Inc. *Investigator:* AbbVie Inc., Boehringer Ingelheim, Celgene Corporation, Novartis Pharmaceuticals Corporation.

M. Alan Menter, MD, *Advisory Board:* AbbVie Inc., Afecta Pharmaceuticals, Inc., Amgen Inc., Boehringer Ingelheim, Eli Lilly and Company, Janssen Biotech, Inc., LEO Pharma Inc., Ortho Dermatologics, Promius Pharma, LLC. *Consultant:* AbbVie Inc., Afecta Pharmaceuticals, Inc., Amgen Inc., Avillion LLP, Boehringer Ingelheim, Eli Lilly and Company, Galderma S.A., Janssen Biotech, Inc., LEO Pharma Inc., Menlo Therapeutics Inc., Novartis Pharmaceuticals Corporation, Ortho Dermatologics, Pfizer Inc., Promius Pharma, LLC. *Investigator:* AbbVie Inc., Amgen Inc., Boehringer Ingelheim, Celgene Corporation, Dermira, Inc., Eli Lilly and Company, Janssen Biotech, Inc., LEO Pharma Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Regeneron. *Speakers Bureau:* AbbVie Inc., Amgen Inc., Janssen Biotech, Inc., LEO Pharma Inc., Ortho Dermatologics, Promius Pharma, LLC.

Address reprint requests to: Jashin J. Wu, MD, Kaiser Permanente Los Angeles Medical Center, 1515 North Vermont Avenue, 5th Floor, Los Angeles, CA 90027; jashinwu@gmail.com

Improving Patient Adherence

Adherence to psoriasis therapy has been traditionally poor. For patients with mild to moderate psoriasis, topical therapy has an especially steep drop-off rate: A survey of 1,200 patients reported that 73% did not adhere to their topical treatment.[1] Clinicians should be aware of the risk for nonadherence as they design and initiate treatment plans.

A key part of the strategy is careful follow-up. For patients with mild to moderate psoriasis who are prescribed topical therapy, a follow-up visit at 1 month is prudent. One study found that, with close monitoring, nonadherence can be reduced from 85% to 51%.[1] In this study (N=40 patients with mild to moderate psoriasis), Alinia and colleagues[1] demonstrated just how lamentable compliance is for 1 year, even for the topical medication fluocinonide ointment. Electronic sensors in the medication cap accurately measured not only the number of times the medication was used but also the dose per use.[1] Adherence was better (although not statistically significant) in the intervention group, in which patients had to submit weekly reports online, vs those in the control group (50% vs 35%, respectively; P=0.08). None of the patients in the study used the medication as directed, and only 15% were adherent during clinical observation. Such findings highlight the need for a better therapeutic alliance between patients and their healthcare team.

To determine why nonadherence is so common, Choi and colleagues[2] surveyed 26 dermatologists and 50 patients. Nearly two-thirds of the dermatologists reported that they spent only 5 to 10 minutes during the first psoriasis treatment consultation. No physician surveyed spent more than 20 minutes, and 54% asked about adherence only 20% of the time during follow-up visits.[2] Patients surveyed said that dermatologists should spend more time explaining their therapy. Approximately one-third did not understand how to use the medications they were prescribed; nearly one-third of patients mistakenly thought the agents would improve their psoriasis in 1 to 2 weeks. More than half (54%) cited lack of efficacy as the chief reason for discontinuing a medication.[2] Clinicians face numerous time constraints, but they need to set patients' expectations about the agents they prescribe. Some of the solutions that patients suggested in this survey are surprisingly simple and include establishing patient support groups, providing education about the incurable nature of psoriasis, and selecting the appropriate agents to align with patients' preferences.[2]

A multinational study of 213 patients with psoriasis concluded that patient preferences on topical vehicles are diverse.[3] Half of the patients in the study preferred the fixed combination of calcipotriol 50 µg/g and betamethasone 0.5 mg/g gel, while the others favored the same formulation in a foam.[3] Both the gel and the foam were also compared with the latest topical treatment (LTT), which patients tended not to prefer if the LTT was an ointment or cream. Patients who preferred the foam said the primary reason was its sensation of immediate relief, while gel users cited the ease of application as the main reason for choosing that vehicle. Clinicians should take the attributes of topical agents into consideration when choosing a therapy for an individual patient: Is it odorless? Does it stain? Does it apply smoothly?

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Mitigating Risks Associated With Psoriasis Treatment

Harm reduction should be a consideration when devising a treatment plan because some therapies need to be monitored more closely than others.

Biologics have warnings about the risk of infection. For example, patients taking biologics should be checked at least annually for tuberculosis with an interferon-gamma release assay or tuberculin skin test (purified protein derivative [PPD]) and other screenings for infections that are specifically mentioned in the label. For example, TNF inhibitors have a boxed warning about lymphoma.

Cumulative toxicity is rare with a biologic, but clinicians must be alert for patients who travel to areas in which tuberculosis, hepatitis C, or hepatitis B are endemic. If patients develop an infection, they need to know when they should call their physician.

A thorough history will help uncover any comorbid depression, a frequently occurring illness with psoriasis and one that is critical to identify before initiating treatment with the phosphodiesterase-4 inhibitor apremilast and the interleukin (IL)-17 inhibitor brodalumab, which both carry warnings about the potential for suicidal behavior.[30,31] If in doubt about patients' psychiatric status, a referral to a psychiatrist to assess their readiness for psoriasis treatment may be appropriate.[32]

When using phototherapy in conjunction with systemic agents, avoid the combination of cyclosporine and phototherapy, particularly psoralen ultraviolet A (PUVA), because that combination can increase the risk of skin cancers.[6]

Patients on methotrexate should take folic acid to reduce adverse effects, such as nausea and vomiting. Asking patients at every visit about their use of any concomitant medications can help avoid potential interactions that increase the risk for methotrexate side effects.[33] Regular creatinine checks are also essential in patients with poor renal function. Methotrexate has been associated with malignant lymphoma and its label carries a boxed warning.[6]

Owing to their fast-acting efficacy and less-frequent administration, biologics do not have the same adherence issues that other psoriasis therapies have.[4] Chan and colleagues[4] found in their study of 106 patients that adherence was nearly 100% for patients taking biologics; adherence rates for oral therapy, phototherapy, and topical therapy were 96%, 93%, and 75%, respectively. Patient-reported attributes that adversely affected adherence included smoking, being busy, and feeling annoyed about their therapy.[4]

Another study (N=200) reported similar findings. Patients with moderate to severe psoriasis preferred biologics, but they differed in the attributes they preferred in therapy: treatment location, efficacy, and probability of adverse effects.[5] Not surprisingly, patients who were employed preferred therapies that offered rapid efficacy, that were convenient, and that required infrequent administration. Older patients in the study were most concerned about adverse effects but were less concerned about efficacy. Overall, more men than women rated efficacy as the most important attribute of a biologic.[5] The results underscore the importance of asking patients what they value most in therapy, eg, rapid results, convenience, risk of adverse effects, or site of treatment (at home or in a clinic).

Once patients and clinicians establish a preferred treatment plan, clinicians should provide patients with written instructions and should set their expectations. It is critical to explain how soon they are likely to see results, what the potential side effects of the regimen are, and when to alert the clinician about adverse events. Patients also need to be aware if clinicians are using off-label dosing, because instructions that differ from product labeling may be confusing.

Combining Topical and Systemic Agents

Aside from patient preferences, treatment decisions are based on disease severity, comorbidities, and symptoms.[6] For patients who are adherent, topical therapies might suffice for mild to moderate psoriasis. Approximately 30% of patients with moderate and 20% of those with severe plaque psoriasis do not have adequate disease control with their current therapeutic regimens because they are receiving only topical therapy when they need more potent drugs.[6]

For patients whose initial monotherapy is proving less effective than predicted, clinicians often consider the use of multiple topical agents or combinations of systemic and topical agents.[6] Combination therapy can provide more rapid efficacy and has the advantage of reducing the dosage of individual agents, thus decreasing the risk for toxicity.[7] Whereas patients with moderate to severe psoriasis need systemic agents or biologics, some might also require localized symptom relief for intractable lesions.[8]

The evidence on combination therapies is scant, but there have been some notable trials. The 16-week BELIEVE trial, which examined the efficacy of the tumor necrosis factor (TNF)–alpha inhibitor adalimumab (ADA) and topical calcipotriol/betamethasone (C/B), found that for the first 4 weeks, combination therapy appeared to be more effective than adalimumab monotherapy (40.7% vs 32.4%, respectively, at week 4 [P=0.021]).[9] At week 16, however, adalimumab monotherapy was slightly better than the combination biologic and topical therapy (64.8% for ADA + C/B vs 70.9% for ADA monotherapy [P=0.086]).[9]

A frequently used combination therapy, again with scant evidence available to support it, is topical calcipotriol/betamethasone and methotrexate.[8] When topical agents are used concurrently as rescue therapy for the face or intertriginous regions in long-term studies of biologics or systemic therapies, their efficacy data are often omitted.[8]

Besides the combinations of systemic agents or biologics plus topical treatments, many topical agents are themselves combined or are used as adjuncts to phototherapy.[8] Evidence is still needed to demonstrate whether synergistic effects of the topical agents might decrease the need for extended periods of phototherapy.[8]

In a systematic review of 66 combination therapies for plaque psoriasis, an overwhelming majority of studies favored combination therapy vs monotherapy.[10] The meta-analysis also found that combining topical therapies, such as vitamin A and D derivatives, was more effective than topical monotherapy. Although it may be common practice, adding a topical agent to a phototherapy regimen did not significantly contribute to plaque clearance.[10]

Fixed-dose combination topical therapies are also widely used because certain formulations are thought to provide complementary effects on psoriasis plaques.[11] Corticosteroids and vitamin D analogues, for example, provide different mechanisms of action that help to clear the lesions. Corticosteroids inhibit inflammation and T-cell activation, and vitamin D analogues reduce the hyperproliferation of keratinocytes and provide homeostasis in the skin.[11] The combination therapy allows for less-frequent

TABLE 1 Drugs and Other Substances That Induce or Exacerbate Psoriasis

Drug Class	Substances and Other Triggers
• Antimalarials[13] • Beta-blockers[13] • Lithium[13] • Nonsteroidal anti-inflammatory agents[13] • Tetracyclines[13]	• Alcohol[17] • Tobacco[17] • Ultraviolet radiation[14]

Sources: Basavaraj KH, et al[13]; Wolf P, et al.[14]

dosing of corticosteroids, which can lead to skin atrophy after long-term use. In a three-arm multicenter study, the combination calcipotriol/betamethasone dipropionate foam was significantly more effective in clearing plaques than were the individual topical agents after 4 weeks of treatment ($P<0.001$).[11]

Combination therapy with a systemic agent plus topical agents can also significantly improve quality of life because topical medications can quickly soothe painful, itchy lesions before the systemic agent can take effect. In a study of 114 patients, Psoriasis Area and Severity Index (PASI) and Psoriasis Disability Index (PDI) scores improved with the systemic agents cyclosporine or methotrexate plus topical clobetasol propionate (0.05%) + salicylic acid (3%) lotion for the scalp and betamethasone valerate (0.05%) cream for the body.[12] The mean quality-of-life scores, as measured by the PDI, were 0.56 ± 0.18 for the topical-only group, 6.53 ± 0.46 for the methotrexate + topical group, and 7.18 ± 0.47 for the cyclosporine + topical group ($P<0.001$). PASI scores were also statistically significant between the topical monotherapy and combination therapy groups ($P<0.001$).[12]

When biologics show a loss of effect, adding methotrexate can boost their efficacy and reduce the anti-drug antibodies against the biologic.[7] In a multinational registry of patients with psoriasis taking biologics, methotrexate was the most frequently used add-on agent. When methotrexate is added to biologics, the 1-year drug survival rate (how long a patient remains on a drug) is similar among the biologics: etanercept, adalimumab, infliximab, and ustekinumab with methotrexate had ranges of 43% to 92%, 28% to 83%, 65% to 87%, and 53% to 77%, respectively.[7] No one biologic was superior to the others when paired with methotrexate. Other therapies used as adjunctive agents with biologics, as recorded in the registries, include acitretin and cyclosporine, with methotrexate having the longest drug survival vs the other agents (103, 78, and 34 months, respectively).[7]

Treatment Considerations—Polypharmacy, Drug Interactions

Patients with psoriasis frequently have comorbidities that must be treated with other drugs, which can complicate treatment (**Table 1**).[13,14] Before initiating treatment and during follow-up visits, clinicians need to take a thorough history to uncover potential drug interactions.

Fortunately, biologics—the mainstays of psoriasis therapy—are relatively free of interactions. The biologics and methotrexate have a favorable risk/benefit profile. Combination therapy allows clinicians to avoid higher doses of any single agent, which can reduce the risk of toxicity. In a meta-analysis of 41 randomized controlled trials (N=20,561 patients with moderate to severe psoriasis), methotrexate and the biologics adalimumab, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab were examined for efficacy relative to their tolerability.[15] Although all the biologics significantly achieved PASI 75 and improved DLQI vs placebo at 12 to 16 weeks, ixekizumab and infliximab were less well-tolerated than the other biologics tested because of serious adverse effects leading to patient withdrawals. Of the agents tested, etanercept and methotrexate were deemed moderately efficacious compared with the other agents in the study.[15]

Before the introduction of biologics, most patients with moderate to severe psoriasis were treated with the systemic agents methotrexate, acitretin, and cyclosporine.[16] Although not as potent as biologics, these systemic drugs had documented serious adverse effects. Long-term use of methotrexate was linked to immunosuppression, bone marrow suppression, and hepatoxicity.[16] Cyclosporine use was associated with hypertension, immunosuppression, and nephrotoxicity.[16] Acitretin use is thought to cause dyslipidemia, cheilitis, and hair loss. Unlike the biologics, the systemic agents each have several drug interactions (**Table 2**).[17,18]

In an effort to reduce the risk of hepatotoxicity while maintaining efficacy, acitretin and methotrexate were tested individually and in combination in 39 patients with plaque psoriasis.[19] As measured by PASI 50 and 75 and DLQI, combination therapy was more efficacious than were the individual acitretin and methotrexate regimens or placebo. Although there were no differences in lesion clearance among the actively treated groups, the combination group had lower histopathologic severity scores than did the individual agent groups. Combination therapy also reduced the risk for liver fibrosis compared with methotrexate alone.[19]

Infections are common in patients taking biologics. Tuberculosis, hepatitis B, hepatitis C, and postoperative infections are among the most prevalent in patients with psoriasis (see "Mitigating Risks Associated With Psoriasis Treatment" on page S54).[6]

TABLE 2 Methotrexate, Cyclosporine, and Acitretin Drug Interactions

Methotrexate Interactions[17]	Cyclosporine Interactions[17]	Acitretin Interactions[18]
• Acitretin • Adapalene • Azathioprine • Bexarotene • Chloramphenicol • Cyclosporine • Etretinate • Isotretinoin • Nonsteroidal anti-inflammatory drugs • Penicillins • Phenylbutazone • Phenytoin • Retinol • Salicylates • Sulfonamides • Tetracyclines • Theophylline • Trimethoprim	• Allopurinol • Amiodarone • Amphotericin • Bromocriptine • Cimetidine • Clarithromycin • Colchicine • Danazol • Diclofenac • Digoxin • Diltiazem • Erythromycin • Fluconazole • Gentamicin • HIV medications • Itraconazole • Ketoconazole • Lovastatin • Melphalan • Methotrexate • Methylprednisolone • Metoclopramide • Naproxen • Nicardipine • Nonsteroidal anti-inflammatory drugs • Potassium-sparing diuretics • Prednisolone or rifabutin • Quinupristin/dalfopristin • Ranitidine • Sulindac • Tacrolimus • Tobramycin • Trimethoprim • Vancomycin • Verapamil	• Alcohol • Corticosteroids • Cyclosporine • Glibenclamide/glyburide • Methotrexate • Minocycline • Oral antidiabetic agents • Phenytoin • Progestogen contraceptives (in mini-doses) • Tetracyclines • Vitamin A (>4,000-5,000 IU/d)

Sources: Saurat JH, et al[17]; Carretero G, et al.[18]

Vaccines

Ideally, patients starting therapy for psoriasis should be up to date on their vaccinations.[20] However, their treatment for psoriasis should not be delayed. In the case of hepatitis B, which requires a series of three vaccinations within a 6-month window, delaying psoriasis treatment could do more harm than good. Clinicians also need to be cautious about vaccinating with live vaccines when patients are on biologics because the immunomodulatory effects could leave patients vulnerable to infection.[20]

Treating the Whole Patient

Psoriasis is a multisystemic disease, and different patients will perceive their illness differently. What some patients may deem a treatment success may be seen by others as a total failure. To some patients, a BSA of <1% could render them inconsolable if the remaining lesions are on their face or in an uncomfortable intertriginous or genital region.

Clinicians are well advised to ask patients what they expect from their treatment and to determine their chief complaints: Is the itching so unbearable that they are losing sleep? What therapies have failed them before? Will comorbidities such as psoriatic arthritis drive the choice of therapy toward biologics? Do they not want pills? Do they not want injections?

Other factors to consider include the patient's age, weight, and pregnancy status. Children have fewer therapy options because methotrexate, cyclosporine, and acitretin do not have specific pediatric indications for plaque psoriasis.[21-23] Several of the biologics, such as etanercept and ustekinumab, have been proved safe and effective in pediatric populations and are approved for pediatric psoriasis by the US Food and Drug Administration (FDA).[24,25] Although some biologics such as adalimumab and infliximab have been approved for juvenile idiopathic arthritis in children as young as 2 years of age and for pediatric Crohn disease, they have not been approved for pediatric plaque psoriasis.[26,27]

In the real world, frequent off-label prescribing occurs. Bronckers and colleagues[24] conducted a retrospective review of children (N=390; mean age, 8.4 years) with moderate to severe psoriasis. Methotrexate was the most commonly used medication (69.2%), followed by biologic agents (mostly etanercept) (27.2%), acitretin (14.6%), and cyclosporine (7.7%). Nearly one in five patients received more than one medication. Of children who were prescribed methotrexate monotherapy, 48% experienced more than one adverse event. Folic acid taken six to seven times per week appeared to alleviate the adverse effects, though there is no consensus on pediatric dosing.[24] Combination treatment, while providing rapid relief to teens and young adults who may be more self-conscious than older patients, could expose young patients to greater toxicity than monotherapy.[6]

Women of childbearing potential or those who are lactating need special consideration when designing a treatment plan for psoriasis. Methotrexate and retinoids like acitretin and tazarotene are teratogenic.[6] Biologics are in pregnancy category B (no adequate controlled studies exist in pregnant women and no animal studies have shown risk to the fetus) and cyclosporine is in category C (animal reproductive studies have shown harm to the fetus and no adequate human studies exist).[6,*] If a woman needs a medication that poses a risk for teratogenicity, she must use two forms of contraception and continue them for 2 years after discontinuing the toxic therapy.[6] As a possible alternative to systemic agents or biologics, phototherapy has yet to record birth defects in women who received such treatment during pregnancy.[29]

* As of June 2015, the FDA no longer uses pregnancy categories A, B, C, D, and X and instead requires a narrative description in the label about data or lack thereof.[28]

Conclusion

Maintaining adherence to a psoriasis regimen starts with a strong therapeutic alliance: individualizing treatment, providing effective education and counseling, setting expectations, and closely following up with the patient. Because psoriasis is a disease with potentially profound detrimental effects on quality of life, one-size-fits-all measures of efficacy, such as PASI, may not fully capture the extent of patients' symptom severity. Clinicians need to consider convenience, lifestyle, location of psoriatic lesions, and comorbidities when tailoring a treatment plan.

References

1. Alinia H, Moradi Tuchayi S, Smith JA, et al. Long-term adherence to topical psoriasis treatment can be abysmal: A 1-year randomized intervention study using objective electronic adherence monitoring. *Br J Dermatol*. 2017;176:759-764.
2. Choi CW, Kim BR, Ohn J, Youn SW. The advantage of cyclosporine A and methotrexate rotational therapy in long-term systemic treatment for chronic plaque psoriasis in a real world practice. *Ann Dermatol.* 2017;29:55-60.
3. Hong CH, Papp KA, Lophaven KW, Skallerup P, Philipp S. Patients with psoriasis have different preferences for topical therapy, highlighting the importance of individualized treatment approaches: Randomized phase IIIb PSO-INSIGHTFUL study. *J Eur Acad Dermatol Venereol*. 2017;31:1876-1883.
4. Chan SA, Hussain F, Lawson LG, Ormerod AD. Factors affecting adherence to treatment of psoriasis: Comparing biologic therapy to other modalities. *J Dermatolog Treat*. 2013;24:64-69.
5. Kromer C, Schaarschmidt ML, Schmieder A, Herr R, Goerdt S, Peitsch WK. Patient preferences for treatment of psoriasis with biologicals: A discrete choice experiment. *PLoS One*. 2015;10:e0129120.
6. Young M, Aldredge L, Parker P. Psoriasis for the primary care practitioner. *J Am Assoc Nurse Pract*. 2017;29:157-178.
7. Busard CI, Cohen AD, Wolf P, et al. Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis: Real-life data from PSONET registries [published online October 17, 2017]. *J Eur Acad Dermatol Venereol.* doi:10.1111/jdv.14583.
8. Wu JJ, Lynde CW, Kleyn CE. Identification of key research needs for topical therapy treatment of psoriasis – a consensus paper by the International Psoriasis Council. *J Eur Acad Dermatol Venereol*. 2016;30:1115-1119.
9. Thaçi D, Ortonne JP, Chimenti S, et al. A phase IIIb, multicentre, randomized, double-blind, vehicle-controlled study of the efficacy and safety of adalimumab with and without calcipotriol/betamethasone topical treatment in patients with moderate to severe psoriasis: The BELIEVE study. *Br J Dermatol*. 2010;163:402-411.
10. Bailey EE, Ference EH, Alikhan A, Hession MT, Armstrong AW. Combination treatments for psoriasis: A systematic review and meta-analysis. *Arch Dermatol*. 2012;148:511-522.
11. Segaert S, Shear NH, Chiricozzi A, et al. Optimizing anti-inflammatory and immunomodulatory effects of corticosteroid and vitamin D analogue fixed-dose combination therapy. *Dermatol Ther (Heidelb)*. 2017;7:265-279.
12. Karamata VV, Gandhi AM, Patel PP, Sutaria A, Desai MK. A study of the use of drugs in patients suffering from psoriasis and their impact on quality of life. *Indian J Pharmacol.* 2017;49:84-88.
13. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. *Int J Dermatol*. 2010;49:1351-1361.
14. Wolf P, Weger W, Patra V, Gruber-Wackernagel A, Byrne SN. Desired response to phototherapy vs photoaggravation in psoriasis: What makes the difference? *Exp Dermatol*. 2016;25:937-944.
15. Jabbar-Lopez ZK, Yiu ZZN, Ward V, et al. Quantitative evaluation of biologic therapy options for psoriasis: A systematic review and network meta-analysis. *J Invest Dermatol*. 2017;137:1646-1654.
16. Armstrong AW, Bagel J, Van Voorhees AS, Robertson AD, Yamauchi PS. Combining biologic therapies with other systemic treatments in psoriasis: Evidence-based, best-practice recommendations from the Medical Board of the National Psoriasis Foundation. *JAMA Dermatol*. 2015;151:432-438.
17. Saurat JH, Guérin A, Yu AP, et al. High prevalence of potential drug-drug interactions for psoriasis patients prescribed methotrexate or cyclosporine for psoriasis: Associated clinical and economic outcomes in real-world practice. *Dermatology*. 2010;220:128-137.
18. Carretero G, Ribera M, Belinchón I, et al; Psoriasis Group of the AEDV. Guidelines for the use of acitretin in psoriasis. Psoriasis Group of the Spanish Academy of Dermatology and Venereology. *Actas Dermosifiliogr.* 2013;104:598-616.
19. An J, Zhang D, Wu J, et al. The acitretin and methotrexate combination therapy for psoriasis vulgaris achieves higher effectiveness and less liver fibrosis. *Pharmacol Res*. 2017;121:158-168.
20. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58:826-850.
21. Methotrexate [prescribing information]. Huntsville, AL: Dava Pharmaceuticals Inc; 2016.
22. Sandimmune (cyclosporine) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.
23. Soriatane (acitretin) [prescribing information]. Research Triangle Park, NC: Stiefel Laboratories Inc; 2017.
24. Bronckers IMGJ, Seyger MMB, West DP, et al; for the Psoriasis Investigator Group (PsIG) of the Pediatric Dermatology Research Alliance and the European Working Group on Pediatric Psoriasis (EWGPP). Safety of systemic agents for the treatment of pediatric psoriasis. *JAMA Dermatol*. 2017;153:1147-1157.
25. Enbrel (etanercept) [prescribing information]. Thousand Oaks, CA: Amgen; 2017.
26. Humira (adalimumab) [prescribing information]. North Chicago, IL: AbbVie Inc; 2017.
27. Remicade (infliximab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2017.
28. US Food and Drug Administration. Pregnancy and lactation labeling (drugs) final rule. December 3, 2014. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm. Accessed February 7, 2018.
29. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. *Can Fam Physician*. 2017;63:278-285.
30. Otezla (apremilast) [prescribing information]. Summit, NJ: Celgene Corporation; 2017.
31. Siliq (brodalumab) [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2017.
32. Wu JJ, Penfold RB, Primatesta P, et al. The risk of depression, suicidal ideation and suicide attempt in patients with psoriasis, psoriatic arthritis or ankylosing spondylitis. *J Eur Acad Dermatol Venereol.* 2017;31:1168-1175.
33. Conway R, Carey JJ. Risk of liver disease in methotrexate treated patients. *World J Hepatol*. 2017;9:1092-1100.