Seminars in Cutaneous Medicine and Surgery

Combining Traditional Agents and Biologics for the Treatment of Psoriasis

Jennifer Clay Cather, MD, and Alan Menter, MD

Psoriasis patients deserve long-term control of their disease with optimal safety. Traditional agents (methotrexate, cyclosporine, retinoids, and photochemotherapy [PUVSI), although providing excellent short-term control, may produce acute or chronic toxicities, thus limiting their usage. Dermatologists are well versed in combination and rotational therapies for psoriasis, using these and other agents. With the advent of biologic therapies (three currently approved, and others pending), the potential for safer long-term psoriasis control is being realized. A review of the literature, plus our personal experience in using combinations of traditional agents and biologics, is presented.
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The prevalence of psoriasis is estimated to be 2% to 3% of the general population. Patients with moderate-to-severe psoriasis, or approximately 25% of all patients, will require phototherapy, systemic therapy, or both for adequate disease control.[1] With the advent of the biologics, the treatment of psoriasis has metamorphosed from intermittent therapy with traditional agents using various treatment strategies (combination, transitional, sequential), influenced largely by cumulative toxicity and adverse events, to continuous therapy with biologics in an effort to obtain longer-term continuous disease control. Additionally, certain biologics have the potential to alter the natural history of psoriasis by limiting or even preventing joint disease progression, as well as providing treatment-free intervals. The transition from traditional agents to biologic agents requires algorithms similar to those established for the combinations commonly used with traditional agents. In this article, we review the literature relating to the use of biologics in combination therapy regimens for the treatment of psoriasis and psoriatic arthritis (PsA), in addition to reporting our experience from our Psoriasis Specialty Clinic (Texas Dermatology Associates) Dallas, Texas.

Combination Data in the Literature

Traditional Agents

The most common systemic traditional agents prescribed for psoriasis worldwide include methotrexate, acitretin, cyclosporine, and psoralen ultraviolet A (PUVA) phototherapy. All these agents have unique safety, tolerability, and convenience issues (Table 1). In the short term, the traditional agents may adequately control disease in most patients. Methotrexate (MTX) was approved for psoriasis by the FDA in 1971; however, to date, no placebo-controlled trials have been performed. A total of 75% of patients obtain a minimum of 50% improvement in their disease.[2] In a recent open-label randomized trial involving 88 patients with chronic plaque psoriasis, 61% of patients treated with MTX and 71% of patients treated with cyclosporine (CyA) obtained a Psoriasis Assessment Severity Index (PASI) score of 75 at week 16.[3] Of note, 12 patients in the MTX group had to discontinue therapy because of reversible liver enzyme elevations, whereas 1 patient in the CyA group discontinued because of elevations in bilirubin levels. In a PsA trial, 35 patients were randomized to either CyA (initiation dose 3 mg/kg/d with escalation up to 5 mg/kg/day) or MTX (initiation dose 7.5 mg/week up to 15 mg/week). After 1 year of therapy CyA and MTX were withdrawn in 41.2% and 27.8% of the patients, respectively (not a statistically significant difference).[4]

Thus, despite excellent efficacy for skin lesions with these 2 entities, safety concerns or side effects often necessitate discontinuation of therapy, underlining the need for alternative agents with more favorable long-term safety profiles. Retinoids frequently show rapid responses within 1 to 2 weeks in patients with erythrodermic and pustular psoriasis; however, patients with chronic plaque psoriasis may take 3 to 4 months to obtain a meaningful response, with just 50% to 60% of patients achieving at least a 50% improvement in PASI scores after 8 weeks of treatment,[5] with the mean PASI improvement after 12 weeks being 70% to 75%.[6] Finally,

Baylor University Medical Center and Texas Dermatology Associates, Dallas, TX.
Address reprint requests to Alan Menter, MD, 5310 Harvest Hill, Suite 260; Dallas, TX 75230. E-mail: amresearch@texasderm.com

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Table 1 Traditional Agents, Time Limits, and Safety Concerns

Medication	Therapy Limits	Safety Concerns
Methotrexate	2 years to first liver biopsy with repeat biopsy every 2 years	Hepatotoxicity, myelosuppression, teratogenicity, immunosuppression, carcinogenicity, pneumonitis
Cyclosporine	1-year limit in US 2-year limit in UK	Nephrotoxicity (1-year limit in US), hypertension, immunosuppression, carcinogenicity
PUVA	Desirable to keep <200 treatments	Immunosuppression, carcinogenicity
Retinoids		Teratogenicity, hyperlipidemia

PUVA is the 1 agent with the potential to induce a remission with more than70% of patients using appropriate regimens (2-4 times a week), obtaining disease-free periods of as long as 6 months. Lifetime treatments need to be kept to less than 200 (or 2000 J/cm^2 UVA) to minimize cutaneous carcinogenicity.

Combination therapy strives to maximize efficacy and minimize toxicity (Table 2). Therapeutics with different modes of action, different kinetics, and different toxicities may be combined to reach this goal.[7] Using different therapies in rotation is logical to decrease the toxicity of any given agent[8]; however, some agents may induce cutaneous malignancies when used in rotation with light (ie, MTX and CyA).[9] The most common combinations include regimens in which retinoids are used to "anchor" or maintain the responses obtained from CyA, MTX, or phototherapy. In addition, retinoids can limit the cumulative exposure to more toxic therapies. For example, combination therapy with retinoids and phototherapy is an attractive regimen because retinoids not only decrease the cumulative UVA or UVB required to obtain a response[10] but also play a role in chemoprevention.[11] Another common strategy used is sequential or transitional therapy, whereby a patient is treated interventionally with a rapidly acting drug (MTX or CyA) and then slowly tapered off the fast-acting drug to a safer medication (retinoid) with a more acceptable safety profile for long-term use,[12,13] In the prebiologic era (January 2003), 850 of our patients with refractory skin and joint disease required combination regimes, eg, MTX and CyA for optimal control of their disease; however, biologics have by and large replaced these more toxic combinations in the majority of our patients (current number of patients on combinations of traditional therapies is 23, as of November 1, 2004).

The mechanism of action of the biologics differs significantly from our traditional therapies; therefore, traditional agents may act synergistically with our traditional agents.[14] Additionally, the biologic drugs as a class lack significant hepatotoxicity, nephrotoxicity, or myelotoxicity, suggesting that they may be safely used with traditional agents in combination regimens. Additive immunosuppression is of concern if the biologics are combined with traditional agents like MTX or CyA, despite data from their use in rheumatologic disorders. In addition, only a small number of psoriasis patients have received long-term monotherapy with biologic agents, eg, 10 courses of alefacept, 36 months of continuous use of efalizumab, and 1 to 2 years for the tumor necrosis factor (TNF)-α antagonists. In general, long-term safety data for psoriasis combination therapy are lacking. Finally, acitretin is not considered to be immunosuppressive and therefore is considered the safest agent to combine with the biologic therapies or to maintain the initial clinical response obtained with a biologic therapy.[15]

Biologic Agents Combined With Traditional Agents

Currently, most combination data involving the biologics are in the setting of cytokine antagonist therapy for rheumatoid arthritis (RA) and, to a lesser degree, PsA.[16] Indication statements found in the prescribing information for the TNF-α agents, including etanercept, infliximab, and adalimumab, permit usage of these therapies in combination with MTX. Although no head-to-head trials have been performed, in general, the aforementioned TNF antagonists appear to have similar efficacy for RA and PsA.[17]

Rheumatology Data

Cytokine Antagonists

Etanercept. In RA, juvenile RA, and ankylosing spondylitis, multiple concomitant medications were administered with etanercept, including MTX, glucocorticosteroids, sulfasalazine, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics (Table 3).[18-23] In the TEMPO trial (Trial of Etanercept and MTX with Radiographic Patient Outcomes), patients on combination therapy showed the most improvement, and at 100 weeks, 86% of patients obtained a 20% improvement in Assessment Score (ACR20).[19]

Table 2 Goals of Traditional Combination Therapy

Lower Dose to Achieve Response	Sequential Therapy to Achieve Quick Response	Rotational Therapy to Avoid Cumulative Toxicity
MTX + CyA	MTX + Retinoid	MTX → Retinoid → UV Repeat
MTX + Retinoid	CyA + Retinoid	
UV + retinoid		

Table 3 Select Etanercept Trials for RA

TEMPO trial	Randomized placebo-controlled study (n = 682) evaluated MTX monotherapy, etanercept monotherapy, and combination therapy with etanercept and MTX. Combination was superior with regards to efficacy and inhibition of radiographic progression
Adult RA	Randomized to etanercept 25 SQ twice weekly, SSZ 2–3 g/day, or etanercept and SSZ for 24 weeks. The adverse events were higher in the combination group compared with the etanercept monotherapy group; however, no differences were noted in infections or blood dyscrasias.[22]

Infliximab. In a 26-week double-blind, placebo-controlled, multicenter trial, 101 patients with RA refractory to low-dose MTX (doses ranged 7.5-15 mg/week) were treated with intravenous infliximab at 1, 3, or 10 mg/kg with or without MTX (7.5 mg/wk) or intravenous placebo plus MTX (7.5 mg/wk) at weeks 0, 2, 6,10, and 14 with follow-up until week 26.[23] In the combination groups, synergistic trends were observed with respect to both efficacy and duration of response, which prompted further evaluation (Table 4).

Additionally, combination of leflunomide with infliximab for RA has been reported by several different groups.[28-30] The combination appears highly efficacious for RA; however, adverse events are common and potentially serious. We have not found leflunomide particularly helpful in our psoriatic patients and studies report conflicting results for both skin and joints.[31,32]

Adalimumab. Clinical trials have been conducted for more than 4 years with adalimumab as monotherapy and in combination with MTX to monitor the long-term efficacy and safety in RA (Table 5). Results from these studies have demonstrated that adalimumab has a rapid onset of action, with sustained efficacy in controlling the signs and symptoms of RA.[33-36] A total of 42% of patients demonstrated no radiologic progression of disease after 2 years of treatment.[37]

In the STAR trial, in the adalimumab treatment group, 82% of patients received concomitant medications, including traditional disease-modifying anti-rhueumatic drugs (as monotherapy or as combination therapy such as MTX [56%], antimalarial drugs [chloroquine or hydroxychloroquine, 23.6%], leflunomide [13.2%], parenteral gold [6%], as well as sulfasalazine [9.2%]) and/or corticosteroids, NSAIDs, and/or analgesics. At 24 weeks, no statistically significant differences were noted between the adalimumab and placebo groups in their respective rates of adverse events (86.5% versus 82.7%), serious adverse events (5.3% versus 6.9%), severe or life-threatening adverse events (11.9% versus

Table 4 Infliximab in Combination Trials for the Treatment of RA

Multicenter placebo-controlled trials		
ATTRACT[24]	428 patients on MTX with refractory RA treated with placebo, infliximab 3 mg/kg or 10 mg/kg at weeks 0, 2, 6, and then every 4 or 8 weeks for 54 weeks	Infliximab groups demonstrated improved QOL, physical function, reduction in radiographic evidence of joint damage (40-55% of patients) along with decreased inflammatory markers compared to the MTX only group
ATTRACT[25]	A 1-year extension of the ATTRACT study n = 259 of which, 216 continued to receive infliximab plus MTX for 102 weeks. (3 or 10 mg/kg) over 102 weeks	40-48% ACR response for infliximab compared to 16% with MTX
Smaller studies		
RA patients (n = 18) who could not tolerate MTX and had active disease on CyA 2 mg/kg and prednisone 5 mg/day[26]		Infliximab was added to baseline regimen at 3 mg/kg and was given at baseline (week 0), 2, 6, and then every 8 weeks thereafter for a total period of 12 months. Efficacy was impressive, 80% of patients obtained an ACR20 and 39% achieved an ACR50
Active RA on MTX (15-17.5 mg/week) and CyA (2.5-3.5 mg/kg/day) (n = 16) combination therapy[27]		Infliximab added after patients randomized to: MTX-CyA (n = 10) or MTX (n = 6). Infliximab was given 3 mg/kg on weeks 0, 2, 6 and then every 8 weeks to both groups. The efficacy at 30 weeks of the MTX-CyA-Infliximab group showed a small statistical advantage compared with the MTX-infliximab group.

Table 5 Adalimumab for RA

Randomized double-blind placebo controlled trials	
STAR trial	**636 patients with refractory RA were treated for 24 weeks with adalimumab 40 mg subcutaneously every other week (n = 318) or placebo (n = 318) in addition to their baseline standard antirheumatic therapy**
ARMADA trial	**271 patients with active uncontrolled RA were maintained on their maximal tolerated dose of MTX (baseline dose range 12.5-25 mg/wk) and randomized to various doses of adalimumab (20, 40, 80 mg subcutaneously every other week) or placebo**

15.4%), or those leading to withdrawal (2.8% versus 2.2%). Also, no statistically significant differences were found in the rates of infections (52.2% versus 49.4%) or serious infections (1.3% versus 1.9%) between the groups.[38] Additionally, there were no lupus-like illnesses over the course of the study despite more adalimumab-treated patients than placebo-treated patients converting from ANA and anti-double-stranded (ds)DNA antibody negative to positive.

On completion of the Anti-TNF Research Study Program of the Monoclonal Antibody D2E& in Rheumatoid Arthritis (ARMADA), Safety Trial of Adalimumab in Rheumatoid (STAR), or 2 phase I trials (DE005 and DE037) patients (n = 843) enrolled in an open-label extension in which they received adalimumab 40 every other week plus MTX. To date, 81% of patients have remained on therapy with 655 patients treated for 24 months, 212 treated for 36 months, and 35 treated for 5 years or more.[39] The rates of severity of adverse events were similar to those observed in the trials.[40]

T-Cell–Modulating Drugs

Alefacept. The efficacy and safety of alefacept in combination with MTX for RA was evaluated in a small randomized, placebo-controlled clinical trial.[41] Patients maintained on their usual dose of MTX were randomized to placebo (n = 12), alefacept 3.75 mg intravenously (IV) weekly (n = 12), and alefacept 7.5 mg IV weekly for 12 weeks (n = 12). In patients treated with the lower dose of alefacept, the ACR20 response rates were 33% at 3 months, 58% at 6 months, and 67% at any time after first dose. Patients on the higher alefacept dose achieved ACR20 rates of 42% at 3 months, 25% at 6 months, and 67% at anytime after first dose. CD4 counts observed in this patient population were similar to those seen in the psoriasis population.

Psoriasis Data: Skin and Joints

Etanercept

Etanercept is FDA approved for both PsA and psoriasis. Trials for PsA allowed patients to be on their baseline concomitant immunosuppressant therapy, including MTX and prednisone. To date, all clinical trials for psoriasis have not allowed concomitant immunosuppressants; therefore, all data are from case reports. In one uncontrolled study, 6 psoriasis patients were treated with etanercept plus MTX (n = 2), acitretin and hydrea (n = 1), acitretin and UVB (n = 1), CyA (n = 1), and calcipotriene (n = 1). All patients improved after etanercept 25mg SC twice weekly was added to their regimen, allowing for lower, and potentially safer, doses of the systemic medications to maintain disease control.

A single case report describes a patient with refractory psoriasis and PsA previously treated with MTX, CyA, concomitant CyA and MTX, and infliximab 5 mg/kg plus MTX 30 mg/week. On discontinuation of MTX, the patient experienced recurrence of disease, which the authors speculated was caused by the formation of neutralizing antibodies to infliximab. Combination therapy with etanercept 25 mg twice weekly and MTX 15 mg weekly resulted in resolution of both psoriasis and PsA.[42]

Another case series has documented the utility of etanercept in combination therapy regimens.[18] The authors report a case of plaque psoriasis (body surface area [BSA] 30%) successfully treated with etanercept plus MTX. Past therapies included MTX and CyA, both of which resulted in little-to-no response; psoriasis was well-controlled with concomitant CyA and MTX, but toxicities precluded further use of this combination. Although an initial worsening was observed when CyA was discontinued, etanercept 25 mg twice weekly along with MTX maintained adequate disease control. Etanercept combinations with acitretin have also been found useful in 2 patients. One patient had plaque psoriasis (BSA 25%), which was previously treated with CyA, MTX, mycophenolate mofetil, and 10 years of PUVA.[18] Combination therapy with etanercept 50 mg twice weekly and acitretin 10 mg daily resulted in clearance of psoriasis within 8 weeks. The second patient, described by Strober and Clarke,[18] was a patient with psoriasis and PsA who developed nephrotoxicity and hypertension on CyA. Etanercept was initiated, CyA was tapered and then discontinued, and the patient maintained on etanercept plus acitretin, initiated at week 16 of etanercept therapy, with resolution of the nephrotoxicity and hypertension.

Infliximab

Infliximab is a chimeric monoclonal antibody that binds soluble TNF-α and cell-bound TNF-α. It was first approved by the FDA in 1998 for Crohn's disease; a year later, infliximab approval was extended to RA in combination with MTX. Currently, this drug is under FDA consideration for the treatment of PsA. This agent has the most impressive PASI 75 responses to date. In an initial pilot study, 88% of patients achieved this endpoint at week 10 after 3 infusions (5 mg/kg) at weeks 0, 2, and 6. A larger study revealed that 3 mg/kg of infliximab was almost equivalent to 5 mg/kg as monotherapy with respect to clearance; however, the higher dose, 5 mg/kg maintained clearness longer. Therefore, most dermatologists prescribing this medication for the treatment of psoriasis use the 5 mg/kg dosage. Because infliximab is a chimeric mole-

cule, antibodies may develop (ATI), which may play a role in infusion reactions and potential dose escalation. Combination therapy may decrease ATIs, as has been shown in RA and Crohn's Disease; however, the experience with combination therapy is limited to case reports. One study reported the safety and efficacy of infliximab in combination with the baseline doses of MTX 15 to 30 mg/week (n = 5) or sulfasalazine 3 g/day (n = 1) for the treatment of skin lesions in patients with PsA.[43] Some concern exits in the literature on RA regarding combining SSZ with infliximab, because SSZ has the ability to promote dsDNA antibodies.

A patient with refractory unstable suberythrodermic psoriasis was treated successfully with infliximab and MTX. The patient's disease was refractory to PUVA (>2000 J/cm^2), CyA, hydroxyurea, azathioprine, etretinate, and acitretin, with little improvement. Eight weeks after a single infusion of infliximab 5 mg/kg combined with MTX 20 mg weekly, the patient was clear.[44,45] Recalcitrant palmoplantar pustular psoriasis has been treated successfully with infliximab plus MTX. Previous therapies included monotherapy or various combinations of MTX, etretinate, acitretin, thioguanine, mycophenolate mofetil, tacrolimus, CyA, PUVA, prednisone, and colchicine.

The successful treatment of severe plaque psoriasis (BSA >50%) with infliximab 5 mg/kg given every 3 months, plus hydroxyurea 1 g daily, in a 49-year-old female with a 35-year history of severe psoriasis and PsA was recently reported.[46] PsA has been treated with infliximab in combination with various medications. In 1 case series (n = 3) infliximab was dosed at week 0, 2, and 6 and then every 8 weeks thereafter. One patient was refractory to MTX-SSZ as well as MTX–etanercept, one patient was refractory to MTX, and the final patient was refractory to MTX plus MTX-SSZ combination therapy. All patients showed improvement of their skin and joints.[47]

Alefacept

The efficacy and safety of alefacept in combination with MTX has been evaluated in PsA.[48] The combination of alefacept and UVB was studied in an open-label study at 2 sites each involving 30 patients. One site used BB UVB[49] and the other used NB UVB.[50] All patients received 12 weekly injections of alefacept 15 mg IM and were randomized (1:1:1) to 1 of 3 UVB groups. At both study sites, group 1 patients received alefacept monotherapy. Group 2 patients received 6 weeks of BB UVB at one site and 6 weeks of NB UVB at the second site. Group 3 patients received 12 weeks of BB UVB at one site and 12 weeks of NB UVB at the second site. A 12-week treatment-free observation period followed the 12 weeks of alefacept dosing. When alefacept was combined with BB UVB, 78% to 80% of patients achieved a 50% or greater PASI reduction compared with 55% of patients who received alefacept monotherapy at some point during treatment or follow-up (24 weeks). When combined with NB UVB, 100% of patients in the study achieved a 50% or greater PASI reduction at some time during treatment or follow-up (24 weeks). The CD4 counts were similar across all treatment groups.

The safety of multiple courses of alefacept (15 mg weekly IM) in combination with other psoriasis medications is currently under evaluation in a large international, open-label study Clinical Long-term Alefacept Repeat Course Intramuscular Therapy Study (CLARITY study).[51] Efficacy of multiple courses of alefacept in combination with other psoriasis therapies: a study that reflects the clinical practice setting. In an initial analysis, 201 patients had entered the first 12-week course of alefacept therapy when 18 had completed the course and were assessed at week 14 (2 weeks post completion of course). Most patients (55%) had moderate-to-severe or severe plaque psoriasis and 35% had PsA Study patients were treated with alefacept alone or in combination with low-potency corticosteroids (n = 96) as well as in combination with mid- or high-potency topical corticosteroids (n = 48), MTX (n = 21), CyA (n = 16), systemic retinoids (n = 10), and UVB (n = 9). Physician Global Assessment improved by at least 1 category (ie, from "moderate to severe" to "moderate") in 61% of patients and at least 2 categories in 32% of patients treated. No unexpected toxicity was noted with any of these combinations—specifically, no liver or renal toxicity was observed. Additionally, the CD4 counts were similar across all treatment groups.

In a pilot study involving 12 patients with moderate-to-severe psoriasis on stable doses of MTX, 83% of patients could be transitioned off MTX onto alefacept by week 8 with no flare-up of their disease.[52] Two patients had to restart MTX—1 patient entered the study on 15 mg of MTX, discontinued at week 9, and restarted 4 months after the last dose of alefacept. The second patient entered the study on 20 mg of MTX, discontinued at week 4, and restarted at week 12 because of worsening of disease. Of the 10 patients that were able to discontinue MTX, 6 achieved improvements from baseline PASI score, with the other 4 maintaining a stable PASI score with alefacept. The CD4 count reductions were consistent with those observed with alefacept monotherapy in other clinical trials. Additionally, routine laboratory studies for renal, hepatic, and bone marrow function were normal. In another pilot study patients were transitioned from CyA to alefacept in 3 phases.[53] During phase I (weeks 1-12) alefacept (15 mg IM weekly IM) was administered with concomitant CyA (baseline dose range 2.2–4.0 mg/kg/d). CyA was tapered and discontinued at week 12. During phase 2 (weeks 13-34) topical agents along with UVB were allowed. Phase 3 (weeks 15-48) entailed 12 weeks of alefacept (15 mg weekly IM) followed by 12 weeks of observation. As before, topicals and UVB were permitted during the observation period. At the time of writing, 11 patients had enrolled and an interim data analysis revealed CD4 count reductions consistent with prior monotherapy studies and no remarkable changes in renal function.

Efalizumab

No combination data exist in the literature. Our personal observations of transitioning patients off traditional therapies (MTX and CyA) onto efalizumab have been positive, with only an occasional case of "flare" of disease and no evident laboratory abnormalities (see later in the section, "Combination Pearls").

Safety Concerns of Traditional–Biologic Combinations

A considerable degree of overlap exists regarding safety concerns with the TNF-α agents. A careful review of systems, review of past medical history and medications, and family history is warranted given the package insert warnings. Thus, new onset neurologic disease (demyelinating disorders in addition to seizure), new onset or worsening of congestive heart disease, opportunistic infections, lymphoproliferative disorders, blood dyscrasias, and autoimmune disorders have all been reported during therapy with these medications. However, years of combination data do not suggest any additive toxicity.[54,55] Autoantibodies, including antibodies against dsDNA, do develop during therapy with etanercept, infliximab, and adalimumab; their significance is unknown at this time.

The largest safety concern shared by patients, physicians, and the FDA alike revolves around concerns of infection and malignancy. Package inserts for infliximab and adalimumab require evaluation for latent tuberculosis (TB) before initiation of therapy. Although a PPD is not required for etanercept, we personally feel this is a baseline test that should be considered, especially in areas of high TB incidence. Patients on immunosuppressants while they have a PPD test must be considered to have a positive result if the erythema and induration is 5 mm instead of the traditional 10 mm. When results are inconclusive, a chest radiograph and pulmonary consultation are helpful. In addition, patients have developed TB on therapy with a prior negative CXR and PPD—new exposure or reactivation of latent infection.

The role of TNF antagonists in the development of lymphoma in RA patients is debated. One study prospectively evaluated 18,572 patients with RA treated with traditional therapies versus TNF antagonists. A causal relationship between RA therapies and the development of lymphoma could not be established; however, the highest rates were with the TNF antagonists, although differences between agents were very small.

Blood dyscrasias have occurred in patients with RA that were treated with etanercept; however, this patient population tends to have more hematologic issues and therefore the causality is unknown. Patients with a history of hematologic abnormalities should be followed carefully and advised to report petechiae, purpura, bleeding, or fever immediately. In a small study of juvenile idiopathic arthritis patients (n = 15), the combination of etanercept with SSZ was associated with leucopenia. Dose reduction of SSZ corrected the leucopenia. In a single case report, a patient with RA on the combination of MTX and infliximab developed disseminated TB, pulmonary aspergillosis, and cutaneous herpes simplex despite chemoprophylaxis with INH.[56]

The effect of infliximab on renal function was reviewed in RA patients on concomitant MTX. Overall, there was no evidence of early or delayed nephrotoxicity 62 weeks after infliximab was initiated, although 3 patients were reported to have creatinine levels greater than 1.3.[57] Hepatotoxicity, although rare, has been observed with infliximab monotherapy as well as combination therapy with MTX. The incidence of hepatotoxicity, primarily a transaminitis greater than three times that of normal, is less than 3%. Additionally, reactivation of hepatitis B in a chronic hepatitis B surface antigen carrier with RA treated with infliximab and low dose MTX has been reported.

In a large placebo controlled trial (n = 428) during the first 54 weeks of therapy, although not statistically significant, upper respiratory infections, sinusitis, pharyngitis, and headache were more commonly seen in the infliximab–MTX combination treatment groups.[24] Lymphoproliferative malignancies, primarily B-cell non-Hodgkin lymphoma associated with Epstein-Barr virus, have been associated with all immunosuppressive therapies, including MTX. An erythrodermic PsA patient treated with CyA and infliximab developed a CD30+ lymphoma, which regressed after the therapies were discontinued.[58] The package inserts for these drugs reports that the rates of lymphoma seen in patients with RA treated with the TNF antagonists is within expected range for RA patients; however, it is above the rate seen in the normal population.

Combination Pearls From Our Clinic

Alefacept

We have used a number of different combinations with alefacept. Patients on a stable dose of a traditional agent (MTX or CyA) are usually tapered off the drug once an early response to alefacept (external clearing) is noted (usually by 6-8 weeks). MTX usually is tapered by 2.5 mg every 3 weeks as long as the disease is stable and CyA tapered by approximately 50 mg every third week. Because acitretin has an acceptable safety profile and plays a beneficial role in chemoprevention, we are not as inclined to discontinue this medication and frequently maintain patients on a low dose (10mg daily) for optimal response. Phototherapy is usually tapered quickly or discontinued completely after week 6.

An analysis of our first 200 patients placed on alefacept is currently underway and will be reported separately. A significant proportion of these patients were on long-term MTX (>1.5 g cumulative) or CyA (longer than 1 year) or on a combination of traditional agents. The goal of transition to alefacept was maintenance of clinical response and reduction of cumulative toxicities from these two agents.

Efalizumab

As with alefacept, for patients on stable doses of traditional agents, tapering usually begins after a response is noted from efalizumab. Although the onset of response is more rapid with this agent compared with alefacept, we still prefer a slow taper off the traditional agent, ie, by week 8 to 16. Fortunately, the most patients respond predictably with discontinuation of the traditional therapy (MTX or CyA); however, some patients may experience new papular lesions in the first 2 to 3 months or inflammatory flares. True rebound is observed in 10% to 14% of patients, especially in nonre-

sponders. Transition trials have been completed to evaluate the ideal combination therapies for patients not responding: superpotent topical corticosteroids, MTX, and CyA are all effective. If a patient develops new-onset papular lesions and is otherwise doing well in the first 2 to 3 months of therapy, disease control usually is obtained with topical corticosteroids. More widespread lesions may require concomitant systemic therapy. Patients who develop an inflammatory flare with no inciting event (change of medication, infection, stress) are treated based on their previous response. If prior response was adequate for disease control, a short overlap with a systemic agent like MTX or CyA is tried. If the patient cannot be tapered off the concomitant agent during the ensuing few months, then efalizumab is abandoned. If the patient is a nonresponder despite 6 to 12 weeks of therapy, then efalizumab is abandoned and the patient is immediately started on an alternative systemic agent. If the patient meets the criteria for rebound (125% baseline PASI) in the setting of no response to efalizumab, we immediately abandon the efalizumab treatment and initiate an alternative systemic such as CyA, MTX, or a retinoid is started immediately. If the patient meets criteria for rebound due to discontinuation of the drug, it may be acceptable to restart efalizumab alone or concomitantly with a traditional systemic such as CyA, MTX, or acitretin.

Etanercept

Most patients with psoriasis show dramatic early responses with 25 mg of etanercept biweekly. However, psoriasis responses are both dose and time-dependent; therefore, when we commence therapy, the dose used is 50 mg twice weekly. In most cases, the "skin response" lags behind the joint response and, hence, we have rarely been able to "step down" to the arthritis dose (25 mg twice weekly) even after 3 months of therapy. We have used all the traditional agents previously described with etanercept. It is commonplace for patients to comment how much better they feel physically on etanercept—its antiinflammatory properties are well described. As with alefacept, we have been able to substantially reduce the dose of traditional agents with concomitant etanercept therapy. In the small percentage of patients whose joints fail to respond to therapy, we switch to either infliximab or adalimumab between weeks 8 and 12. In patients with a less than optimal skin response in the 50mg biweekly dosage schedule, despite the addition of a traditional agent, a switch is made to either infliximab or adalimumab.

Infliximab

Infliximab is the only biologic that allows for abrupt discontinuation of a patient's baseline MTX or CyA with few concerns about potential flares or rebound once therapy with infliximab is initiated. With regular dosing every 6 to 8 weeks, concomitant MTX does not appear to be required to block the formation of anti-infliximab antibodies in most psoriasis patients. Some patients appear to slowly lose their response to the drug; however, most patients are able to maintain excellent clearing with the same dosing regimen throughout therapy. We also have used infliximab in some patients, especially those from far a field, for rapid clearing (3-4 doses) and then converted them to home administration with etanercept or adalimumab without difficulty. Etanercept is usually commented within 2 to 4 weeks of the last infliximab infusion and adalimumab within 4 to 6 weeks. In the few patients who lose response to infliximab treatment, despite shortening the interval between infusions, we have added low dose MTX (7.5 mg/week) with gratifying responses.

Adalimumab

Like infliximab, adalimumab responses have a fast onset; therefore, patients can usually be tapered off of their traditional agents, MTX and CyA, more quickly than with etanercept. We commonly use the 40-mg weekly dosage initially, and even after discontinuation of the MTX or CyA, are able to reduce the dose of adalimumab in many patients to the more traditional rheumatologic dosing schedule of every other week while maintaining clinical response.

Conclusions

Dermatologists have had a great deal of experience with the use of traditional nonbiologic agents as monotherapy, eg, MTX, CyA, retinoids, phototherapy, and photochemotherapy. All these agents also have been used in various combinations ever since MTX was first approved for psoriasis in 1971. With the recent advent of the biologics, dermatologists will be renewing their interest in combination therapies using the biologic agents together with the aforementioned traditional therapies. We are fortunate in having a great deal of data available to us, particularly safety-related, on the use of biologics, in particular TNF-α agents, in combination with various modalities, particularly MTX, in the rheumatology and gastroenterology literature. Diseases such as RA and Crohn's disease have inherently more comorbidity associated with them than does psoriasis, suggesting that combination therapies with these biologic agents and our traditional agents in our psoriasis population should prove to be, if anything, safer than in RA or Crohn's disease patients. Dermatologists are now recognizing the tremendous quality of life impact that psoriasis has on our patients, as discussed by Feldman in this issue. Thus, maintaining psoriasis in relative remission during the course of an individual patient's lifetime should be a priority when treating moderate-to-severe psoriasis.

The old paradigm of short courses of treatment with discontinuation as the result of concerns regarding organ toxicities, ie, bone marrow and hepatic with MTX and renal and hypertension with CyA, as well as mucocutaneous, lipids, and teratogenicity with retinoids, surely has to change, particularly as dermatologists become more comfortable with the biologic agents. However, our traditional therapies will not be abandoned, particularly in countries lacking the financial resources to expend on biologic agents. Therefore, it is incumbent on dermatologists to develop algorithms for cost-

effective long-term therapy, in which biologics as well as traditional agents (MTX, CyA, particularly retinoids) and phototherapy all play a role. This is a daunting task, but one that already is being tackled by thought leaders in the psoriasis arena. We owe it to our patients, together with providing leadership to third-party payers, to establish these guidelines. Dermatologists, as experts in combination therapy, will hopefully be up to the task in accomplishing this. Finally, as PsA may potentially affect up to one third of our psoriasis patients, dermatologists will need to work with rheumatologists to develop guidelines for optimal combination use, including even the use of traditional nonsteroidal antiinflammatory drugs for our patients with PsA. Again, initial meetings between dermatologists and rheumatologists already have been undertaken with positive outcomes. Combining traditional agents with biologics will allow dermatologists to continue to play a key role in maintaining the quality of life of our patients with psoriasis and PsA.

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