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# From the Medical Board of the National Psoriasis Foundation: Monitoring and vaccinations in patients treated with biologics for psoriasis

Mark Lebwohl, MD,<sup>a</sup> Jerry Bagel, MD,<sup>b</sup> Joel M. Gelfand, MD, MSCE,<sup>c</sup> Dafna Gladman, MD,<sup>d</sup> Kenneth B. Gordon, MD,<sup>e</sup> Sylvia Hsu, MD,<sup>f</sup> Robert E. Kalb, MD,<sup>g</sup> Alexa Boer Kimball, MD, MPH,<sup>h</sup> Neil J. Korman, MD, PhD,<sup>i</sup> Gerald G. Krueger, MD,<sup>j</sup> Philip Mease, MD,<sup>k</sup> Warwick L. Morison, MD,<sup>l</sup> Amy Paller, MD,<sup>m</sup> David M. Pariser, MD,<sup>n</sup> Christopher Ritchlin, MD,<sup>o</sup> Bruce Strober, MD, PhD,<sup>p</sup> Abby Van Voorhees, MD,<sup>q</sup> Gerald D. Weinstein, MD,<sup>r</sup> Melodie Young, MSN, RN,<sup>s</sup> and Liz Horn, PhD<sup>t</sup>

*Toronto, Ontario, Canada; New York, Rochester, and Buffalo, New York; Cleveland, Ohio; Baltimore, Maryland; Irvine, California; Dallas, Texas; Portland, Oregon; Boston, Massachusetts; Chicago, Illinois; Norfolk, Virginia; Philadelphia, Pennsylvania; and Salt Lake City, Utah*

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From the Department of Dermatology, Mount Sinai School of Medicine<sup>a</sup>; Dermatology, The College of Physicians and Surgeons of Columbia University<sup>b</sup>; Department of Dermatology<sup>c</sup> and Center for Clinical Epidemiology and Biostatistics,<sup>c</sup> University of Pennsylvania; Centre for Prognosis Studies in the Rheumatic Diseases, University Health Network, Toronto Western Hospital<sup>d</sup>; Division of Dermatology, Loyola University Medical Center<sup>e</sup>; Department of Dermatology, Baylor College of Medicine<sup>f</sup>; Department of Dermatology, SUNY at Buffalo School of Medicine<sup>g</sup>; Massachusetts General and Brigham and Women's Hospitals, Harvard University<sup>h</sup>; Department of Dermatology and the Murdough Family Center for Psoriasis, Case Western Reserve University/University Hospital of Cleveland<sup>i</sup>; Division of Dermatology, University of Utah Medical School<sup>j</sup>; Rheumatology, University of Washington School of Medicine<sup>k</sup>; Dermatology, Johns Hopkins University, Baltimore<sup>l</sup>; Department of Dermatology, Northwestern University's Feinberg School of Medicine<sup>m</sup>; Department of Dermatology, Eastern Virginia Medical School<sup>n</sup>; University of Rochester School of Medicine and Dentistry<sup>o</sup>; Department of Dermatology, New York University School of Medicine<sup>p</sup>; Department of Dermatology, University of California, Irvine<sup>q</sup>; Private practice, Dallas<sup>r</sup>; and National Psoriasis Foundation, Portland.<sup>t</sup>

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Correspondence to: National Psoriasis Foundation, 6600 SW 92nd Ave, Suite 300, Portland, OR 97223-7195. E-mail: [getinfo@psoriasis.org](mailto:getinfo@psoriasis.org).  
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**Background:** Biologics are widely used in the treatment of psoriasis and psoriatic arthritis.

**Objective:** Our aim was to arrive at a consensus on the kind of monitoring and the vaccinations that should be performed before and during biologic therapy.

**Methods:** Medical literature and data presented at meetings were reviewed and a consensus conference was held by members of the Medical Board of the National Psoriasis Foundation.

**Results:** Consensus was established on monitoring and vaccination practices that included discussion and recognition of variations in those practices. History, physical examination, chemistry screen with liver function tests, complete blood cell count, and platelet count and tuberculosis testing are widely obtained at baseline and with variable frequencies thereafter. Patients treated with efalizumab have platelet counts checked more often; liver function tests are repeated more frequently in patients treated with infliximab; patients taking tumor necrosis factor blockers undergo tuberculosis testing more often; and patients treated with alefacept have CD4 counts checked approximately every 2 weeks. Avoidance of live vaccines during biologic therapy and administration of essential vaccines before biologic therapy were discussed, although vaccination is performed only to a variable degree. There was no consistency in the measurement of antinuclear antibodies among the experts.

**Limitations:** There are few evidence-based studies on monitoring practices for patients with psoriasis taking biologic therapies.

**Conclusions:** In patients taking biologic therapies for psoriasis, monitoring of blood chemistries, blood counts, CD4 counts, antinuclear antibodies, tuberculin skin tests, history, and physical examination may be warranted depending on the particular therapy and the particular patient. Vaccination practices are also addressed. (J Am Acad Dermatol 2008;58:94-105.)

With the introduction of biologic agents, the treatment of psoriasis has changed dramatically. Biologics now account for a significant proportion of systemic therapies used for psoriasis.<sup>1,2</sup> There are few data, however, on the type or frequency of monitoring for optimal safety. Biologic therapies target specific portions of the immune system and, thus, offer the promise of being less immunosuppressive than therapies that broadly suppress the immune system. However, because we do not yet have many years of experience we need to be vigilant in monitoring patients taking these agents.

Biologics have associated side effects that warrant monitoring, and the need for monitoring guidelines in patients treated with biologics has been noted in a survey of rheumatologists.<sup>3</sup> An equally important question pertains to efficacy and safety of vaccination while on these agents. There are few or no evidence-based studies examining the merits of monitoring patients taking biologic therapies.

A survey of members of the Medical Board of the National Psoriasis Foundation found great variation in the frequency and type of monitoring performed for patients treated with biologics.<sup>4</sup> Because formal guidelines can take years for proper development,<sup>5</sup> we generated a consensus statement on safety

monitoring and vaccinations to assist our colleagues until formal guidelines are developed. These are not intended to establish a standard of care, but rather to present a discussion of monitoring practices used by individuals with substantial experience in biologic therapy of psoriasis.

## METHODS

Members of the Medical Board of the National Psoriasis Foundation were surveyed about their monitoring and vaccination practices before patients with psoriasis are started on biologics. The survey also asked about the type and frequency of monitoring performed during therapy. The results of those surveys are reported in a separate article and were used as a basis for a consensus conference of the Foundation's medical board.<sup>4</sup> In preparation for our consensus conference, we reviewed medical literature (gastroenterology, rheumatology, dermatology, and transplantation) pertaining to appropriate monitoring and vaccinations in patients taking biologics specifically and immunosuppressive agents in general. Literature searches on PubMed listed each of the biologic agents and the tests considered or key search terms regarding potential side effects (heart failure, cardiac, demyelinating, multiple sclerosis, infection,

malignancy, lymphoma, squamous cell carcinoma, anemia, leukopenia, neutropenia, thrombocytopenia, pancytopenia, hepatitis, lupus, tuberculosis, and vaccine). Our literature review included poster presentations at scientific meetings and the package inserts for the relevant drugs.

We also discussed the clinical experience of rheumatologists and dermatologists in treating patients with psoriasis or psoriatic arthritis with biologic agents. Members of our medical board include dermatologists, rheumatologists, and a dermatology nurse.

Our consensus was formulated at the medical board meeting of the National Psoriasis Foundation on February 1, 2007, in Washington, DC. This was followed by open e-mail discussions about the proposed monitoring and vaccination recommendations and a teleconference call on February 14, 2007. Recommendations were incorporated into a final document that was sent to the medical board for approval.

## RESULTS

### History and physical examination

The need for history and physical examination was assessed. Elements brought into focus included medical history for tuberculosis (TB) exposure, other chronic infections, malignancy, and a review of systems (specifically neurologic, cardiac, and musculoskeletal [psoriatic arthritis]). Neurologic history is relevant as tumor necrosis factor (TNF)- $\alpha$  inhibitors can rarely be associated with new onset or exacerbation of demyelinating diseases such as multiple sclerosis and should, therefore, be avoided in patients with multiple sclerosis or those at increased risk for developing multiple sclerosis.<sup>6-17</sup> Unpublished anecdotal reports of Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy in patients treated with efalizumab have recently come to light and, if borne out, may impact selection of therapies in patients with neurologic diseases.

A history of heart disease or congestive heart failure may be relevant as well. There have been reports of new onset congestive heart failure in patients treated with TNF inhibitors.<sup>18</sup>

One small study showed an increase in deaths or hospitalizations in patients with congestive heart failure treated with high-dose (10 mg/kg) infliximab.<sup>19</sup> In that study, conventional doses of infliximab (5 mg/kg) did not result in more deaths or hospitalizations. Studies with other TNF inhibitors have yielded mixed results.<sup>20-25</sup> In a Department of Veterans Affairs study of 303 patients that examined the incidence of new onset congestive heart failure or heart failure exacerbations, 6.7% of patients with

rheumatoid arthritis on TNF inhibitors were admitted for congestive heart failure compared with 8% of control patients with rheumatoid arthritis.<sup>26</sup> These findings call into question whether or not TNF inhibitors exacerbate congestive heart failure.

Routine history and physical examination may also uncover clues about infection or malignancy, both important considerations for patients undergoing treatment with any drug affecting the immune system. The package inserts for biologics advise caution on treating patients with a history of malignancy, who develop malignancy, or who have active infection.<sup>27-31</sup> Concern has been raised about the possible association between TNF inhibitors and lymphoma,<sup>32-37</sup> although this association remains controversial.<sup>38-40</sup> There have also been reports of patients taking TNF inhibitors developing squamous cell carcinoma of the skin,<sup>41-43</sup> but a 5-year review of patients with rheumatoid arthritis treated with etanercept did not show an increase in cutaneous squamous cell carcinoma.<sup>44</sup>

To look for any relevant signs or symptoms, history and physical examination can be performed by dermatologists or rheumatologists, or recommendations simply made that patients have routine follow-up examinations by primary care physicians. Signs or symptoms related to liver, neurologic, or cardiac disease; infection; or malignancy are relevant if biologics therapy is contemplated or undertaken. There was consensus that psoriasis and psoriatic arthritis should be assessed at baseline and in the course of therapy to evaluate response to treatment.

### Hematology

Anemia, leukopenia, neutropenia, thrombocytopenia, pancytopenia, and aplastic anemia have been reported rarely with TNF blockers<sup>29-31,45-52</sup>; autoimmune pancytopenia has been reported with efalizumab<sup>45</sup>; and thrombocytopenia was noted in early clinical trials in 8 of 2700 patients treated with efalizumab.<sup>28</sup> In the latter trials, thrombocytopenia was defined as platelet counts at or below 52,000. Onset of platelet decline occurred 2 to 3 months after the first dose of efalizumab. Of note, there were other possible causes of thrombocytopenia in some of the patients enrolled in efalizumab trials. For example, patients may have been treated with methotrexate with resulting hepatic fibrosis, portal hypertension, and hypersplenism. Of the 8 reported patients, 5 were treated with systemic steroids. Thrombocytopenia resolved between 35 and 112 days in 7 of the 8 patients. One of the patients was lost to follow-up.<sup>28</sup>

Because of potential for associated hematologic abnormalities, there was general agreement that

baseline complete blood cell count should be considered before starting biologic therapy. Repeated complete blood cell count with platelet count can be considered monthly for the first 3 to 6 months in patients being treated with efalizumab, and every 2 to 6 months in patients taking adalimumab, etanercept, or infliximab. Because alefacept can result in a reduction in CD4<sup>+</sup> counts, it is currently recommended that this test should be monitored at least every 2 weeks during the 12-week course of alefacept therapy. CD4<sup>+</sup> counts can be checked at the time of intramuscular injection of alefacept and the following week's dose of alefacept can be delayed if CD4<sup>+</sup> counts decrease below 250 cells/ $\mu$ L.

### **Chemistry screen with liver function tests**

There have been isolated reports of hepatotoxicity in patients treated with alefacept, efalizumab, adalimumab, and etanercept, but these are reported so uncommonly that it is not clear whether liver toxicity can be ascribed to these drugs. In addition, small increases in liver function test results have been found in clinical trials of the aforementioned biologic agents, but the increases have seldom necessitated discontinuation of the drug. For example, in a 24-week trial of alefacept, 1.7% of treated patients developed a 3-fold or higher increase in transaminases compared with 1.2% of patients treated with placebo.<sup>27</sup> Similarly, in efalizumab pivotal trials, elevation in two or more liver function tests occurred in 3.1% of patients treated with efalizumab compared with 1.5% of patients treated with placebo.<sup>28</sup>

The frequency and severity of liver complications in patients treated with infliximab is of greater concern.<sup>53,54</sup> In psoriatic arthritis studies, elevations of alanine aminotransferase occurred in 49% of patients treated with infliximab compared with 16% of patients treated with placebo. In 5% of those patients, alanine aminotransferase was greater than or equal to 3 times the upper limit of normal, and in 2% it was greater than or equal to 5 times the upper limit of normal.<sup>30</sup> Acute liver failure, jaundice, hepatitis, and cholestasis have been reported in patients treated with infliximab. Autoimmune hepatitis was the cause in some of these cases.<sup>30</sup> The onset of signs or symptoms of liver disease occurred as early as 2 weeks after the first infusion, but more than 1 year after the first infusion in other cases. In some cases the liver disease was fatal or required liver transplantation.

There was uniform agreement on the need for a baseline chemistry screen in patients treated with any of the biologic agents. There was substantial variability in the frequency of monitoring chemistry screens, but the majority of medical board members

check chemistry screens at intervals varying from 2 to 6 months in patients taking biologic agents. Liver function tests certainly should be checked in patients with signs or symptoms of liver toxicity, and attempts should be made to find the underlying cause. In patients treated with infliximab, many obtain liver function tests at the time of the infusion. If these findings are elevated, repeated liver function tests should be performed before subsequent infusions to gauge safety of proceeding with therapy. Treatment should be withheld in patients with transaminase levels greater than or equal to 5 times the upper limit of normal. Some members of the medical board obtain liver function tests several days before each infliximab infusion, although many check blood tests only at the time of the infusion. Monitoring of liver function tests was thought to be less essential in patients taking the other biologic agents, but the majority still obtained chemistry screens at 6-month intervals in patients taking continuous treatment. Baseline chemistry screens were repeated only at the start of each course of alefacept by most advisors.

Reactivation or worsening of hepatitis B has been reported in patients treated with infliximab and with the other TNF inhibitors.<sup>29,31,55-59</sup> Individual members of the medical board check serologies for hepatitis B before initiating biologic therapy, but others do not routinely check for hepatitis B or C unless warranted by elevated liver function test results or other signs, symptoms, or known risk factors.

### **Antinuclear antibodies**

Antinuclear antibodies including antidouble-stranded DNA, antihistone, anti-Sm, and antiribonucleoprotein antibodies, and others have been reported in patients treated with TNF inhibitors.<sup>29-31,60-73</sup> In rare instances, lupuslike syndromes have been reported in patients treated with TNF inhibitors and in some cases the syndromes resolve on discontinuation of the TNF blocker.<sup>74-92</sup> Conversely, TNF blockers have been used to successfully treat systemic lupus erythematosus.<sup>93-96</sup>

The presence of serum antinuclear antibodies is not specific for systemic lupus erythematosus and by itself is not a contraindication to treatment with TNF inhibitors. Consequently, only a minority of medical advisors check antinuclear antibodies before starting therapy with TNF inhibitors. Once treated with TNF inhibitors, antinuclear antibodies commonly develop and do not require interruption of therapy. For that reason, the large majority of advisors agree that they would not recommend obtaining follow-up antinuclear antibody assays once TNF inhibitor therapy is started, unless other signs or symptoms of lupus developed.

### Testing for TB

TNF is necessary for the development of the granulomatous response,<sup>97</sup> and cases of TB have been reported in patients treated with all the TNF blockers.<sup>98-117</sup>

Specifically, there has been an increase in TB in patients treated with infliximab and in patients treated with adalimumab, especially in trials conducted in Europe and before the time when TB skin test screening was introduced routinely in clinical trials. The package inserts for the latter two agents recommend skin testing for TB before initiating therapy.<sup>30,31</sup> Although the numbers of patients who have developed TB in etanercept trials may not be increased, extrapulmonary cases of TB have been reported in patients treated with etanercept.<sup>112,113</sup> The Centers for Disease Control and Prevention recommend TB testing before starting treatment with any TNF blocker.<sup>117</sup>

In patients with positive TB skin test findings, chest radiographs are usually obtained and patients may be referred to appropriate specialists for treatment of latent TB if chest radiograph findings are negative. In individuals with positive TB skin test results related to BCG vaccination, new blood tests that measure the production of interferon on stimulation with TB antigens not present in BCG may be helpful.<sup>118-120</sup>

Reactivation of TB is not just a problem for TNF inhibitors, as this complication may be seen with other immunosuppressive therapies as well. There are well-documented cases of reactivation of latent TB in patients treated with methotrexate<sup>121,122</sup> and with cyclosporine.<sup>123</sup> More than 90% of those surveyed perform TB skin testing with the TNF inhibitors. Efalizumab and alefacept have not been associated with the reactivation of latent TB, but they are immunosuppressive and, as a result, the majority of advisors perform baseline TB skin testing before therapy with those agents as well.

Although package inserts for the TNF inhibitors do not mandate annual testing for TB, a majority of those surveyed do perform annual TB skin testing in patients taking TNF inhibitors, particularly patients at risk such as health care workers or those who travel to areas where TB is common, and many perform the test annually in patients taking alefacept and efalizumab as well. With the information available, physicians may wish to consider annual TB testing in patients taking any immunosuppressive therapy.

### Vaccinations

Because biologic therapies target the immune system, any steps that can be taken to prevent infection, such as vaccinations, should be considered.

However, the possibility that biologic therapies impair the immunologic response to vaccinations must also be considered. There is little evidence-based medicine to demonstrate that vaccination of patients treated with biologics prevents or reduces the severity of subsequent infection. Likewise, there is little evidence to show that vaccinations are not effective in patients receiving biologics.

In a small clinical study, intravenous efalizumab at a dose of 0.3 mg/kg given before primary immunization reduced the antibody response to that immunization.<sup>28</sup> The 0.3-mg/kg intravenous dose is comparable with the conventional 1-mg/kg subcutaneous dose. Antibody responses to tetanus toxoid were also decreased in a chimpanzee model treated with efalizumab.<sup>28</sup> The package insert, therefore, cautions against vaccination during treatment. In contrast, patients treated with alefacept had normal responses to tetanus toxoid and to primary vaccination with a neoantigen.<sup>124</sup>

A number of studies have looked at immunologic responses to vaccinations in patients treated with etanercept and other TNF blockers. Humoral immune responses to pneumococcal vaccination, for example, are substantial, but titers may be lower than those achieved in patients not treated with etanercept.<sup>125-127</sup> Studies of humoral immunologic response to influenza vaccine in patients treated with TNF blockers demonstrated responses that were good, but less than in those not treated with TNF blockers.<sup>128,129</sup> Similarly, patients treated with adalimumab were effectively immunized with pneumococcal and influenza vaccines.<sup>130</sup> In a study of 64 patients with rheumatoid arthritis, there was no evidence that adalimumab suppressed delayed-type hypersensitivity or immunoglobulin levels.<sup>31</sup> Data on vaccination responses in patients treated with infliximab are limited, but like the other TNF blockers, adequate but reduced immune responses may occur.<sup>131</sup>

In considering vaccinations for patients to be treated with biologic agents, we can learn from our transplant colleagues.<sup>132</sup> Standard vaccinations (Table I)<sup>133</sup> are recommended before transplantation and initiation of immunosuppressive therapy. Once immunosuppressive therapy has begun, patients are advised to avoid vaccination with live and live-attenuated vaccines.<sup>134,135</sup> Package inserts for some of the biologics carry similar information. In patients with juvenile rheumatoid arthritis, for example, vaccinations are recommended before starting etanercept<sup>29</sup>; and the same practice is recommended before starting infliximab for patients with Crohn's disease.<sup>30</sup> The package insert for efalizumab cautions against any vaccinations.<sup>28</sup>

**Table I.** Adult immunization recommendations approved by the Advisory Committee on Immunization Practices, the American College of Obstetrics and Gynecology, and the American Academy of Family Physicians<sup>133</sup>

| Vaccine                                 |  |
|---|--|
| Tetanus, diphtheria, pertussis          | Administer to all persons who lack evidence of immunity.* Booster is recommended every 10 y.   |
| Human papillomavirus                    | 3 Doses recommended for women and girls < age 26 y.  |
| Measles, mumps, rubella                 | Recommended for individuals < age 50 y who lack evidence of immunity and for selected individuals at high risk > age 50 y.   |
| Varicella                               | Vaccine recommended for individuals < age 50 y who lack evidence of immunity and for selected individuals > age 50 y. Note that this is a live vaccination that should not be administered to patients already taking biologics. |
| Herpes zoster                           | For selected individuals $\geq$ age 60 y. Note that this is a live vaccine that should not be administered to patients already taking biologics.   |
| Influenza                               | For selected <sup>†</sup> individuals < age 50 y and for individuals $\geq$ age 50 y annually. Note that inactivated influenza vaccine should be used for patients already taking biologics.                                     |
| Pneumococcal polysaccharide vaccination | For selected individuals < age 65 y and for all individuals $\geq$ age 65 y who lack evidence of immunity.   |
| Hepatitis A                             | For selected individuals at high risk.   |
| Hepatitis B                             | For selected individuals at high risk.   |
| Meningococcal vaccination               | For selected individuals at high risk.   |

\*Theoretic reasons for vaccination are agreed on by members of this consensus conference, but there was variation in the vaccination practices of participating experts.

<sup>†</sup>Several, but not all, experts advocate annual influenza vaccination in patients taking biologic agents.

Some of our advisers vaccinate patients with the pneumococcal vaccine and others, the vaccine for hepatitis B. Many do not recommend vaccinations routinely and point out that patients with biologics have not been shown to have higher incidences of influenza or pneumococcal pneumonia. Of interest, approximately 50% of surveyed experts advise their patients to have influenza vaccines annually. Certainly, it is preferable to start vaccinations before initiation of biologic therapy if vaccinations are to be administered. Significant antibody production occurs within 2 weeks of primary immunization, although peak production may take longer than 6 weeks. It is not always practical to wait to initiate biologic therapy and, therefore, practices vary.<sup>124</sup> If patients are in treatment with biologic therapies, physicians can consider administering influenza vaccination or other vaccinations as long as live vaccines are avoided.

## DISCUSSION

Most studies of monitoring and vaccination practices in patients treated with biologics are not evidence based, making it difficult to create monitoring guidelines. There are few double-blind, placebo-controlled studies to show that monitoring or vaccinations prevent complications or disease. Several

well-done studies help us predict which interventions are likely to find abnormal results. For example, pivotal trials with biologics were large enough to detect small numbers of cases of thrombocytopenia in patients treated with efalizumab, and infliximab trials showed increase in liver function test results compared with patients treated with placebo. Likewise, well-done immunization studies predict which patients are likely to develop antibody responses to injected antigens, but do not demonstrate that immunization with vaccines protects against disease in patients treated with biologics. One thoughtful article made reasonable monitoring suggestions based on one center's experience using biologic therapies.<sup>136</sup>

Some of the studies cited report the results of published clinical trials. Others are taken from data in the package inserts of the 5 approved biologics. The latter inserts are based on data from large double-blind, placebo-controlled pivotal trials. For example, the package inserts for infliximab and adalimumab recommend skin testing for TB. Our consensus conference statement differs in that we suggest considering testing for TB in patients taking etanercept, alefacept, and efalizumab as well.

Recommendations for monitoring or vaccinations that are mentioned in package inserts are reviewed

**Table II.** Key monitoring and vaccination recommendations in product package inserts

| Biologic   | Monitoring recommendations  | Vaccination recommendations  |
|------------|---|--|
| Adalimumab | Tuberculin skin test before therapy   | Avoid live vaccines  |
| Alefacept  | CD4 <sup>+</sup> T-lymphocyte counts before and every 2 wk during each 12-wk course   | Live or live-attenuated vaccines not studied; response to tetanus toxoid and experimental neoantigen preserved |
| Efalizumab | Platelet counts every month on initiation of therapy and eventually every 3 mo  | Acellular, live, and live-attenuated vaccines should not be given while on efalizumab                          |
| Etanercept |   | Immunize before initiating etanercept; patients may receive concurrent vaccines except for live vaccines       |
| Infliximab | Tuberculin skin test before starting therapy; patients with signs or symptoms of liver dysfunction should be evaluated for evidence of liver injury | Immunize before initiating infliximab; avoid live vaccines   |

Note that monitoring recommendations in package inserts may be incomplete.

**Table III.** Tests and vaccinations to consider when treating patients with biologic agents for psoriasis

| Hematology CBC + Plt                              | Chemistry screen with LFTs                                      | ANA         | TB skin test    | Vaccinations                              |
|---|---|-------------|-----------------|---|
| Adalimumab  | BL  | BL optional | BL and annually | BL standard vaccinations*                 |
| BL and every 2-6 mo                               | Every 2-6 mo  |             |                 | Annual inactivated influenza              |
| Alefacept   | BL  |             | BL and annually | BL standard vaccinations*                 |
| CD4 <sup>+</sup> BL and every 2 wk during therapy | At beginning of each course and for any signs of hepatic injury |             |                 | Annual inactivated influenza              |
| Efalizumab  | BL  |             | BL and annually | BL standard vaccinations*                 |
| BL  | Every 2-6 mo  |             |                 | Annual inactivated influenza <sup>†</sup> |
| Monthly × 3-6 mo then every 3 mo                  |   |             |                 |   |
| Etanercept  | BL  | BL optional | BL and annually | BL standard vaccinations*                 |
| BL  | Every 2-6 mo  |             |                 | Annual inactivated influenza              |
| Every 2-6 mo                                      |   |             |                 |   |
| Infliximab  | BL  | BL optional | BL and annually | BL standard vaccinations*                 |
| BL  | Every 2-6 mo  |             |                 | Annual inactivated influenza              |
| Every 2-6 mo                                      |   |             |                 |   |

These are based on review of the literature and survey of practitioners with expertise in the use of biologic agents. Note that there was variation in the frequency and type of tests ordered by those participating in the consensus conference, and these tests and vaccinations should, therefore, not be viewed as mandatory.

ANA, Antinuclear antibodies; BL, baseline (before initiating therapy); CBC + Plt, complete blood cell count and platelets; LFTs, liver function tests; TB, tuberculosis.

\*When practical.

<sup>†</sup>Package insert advises against vaccines in patients taking efalizumab based on data demonstrating a reduction in antibody response to vaccination. Nevertheless, a sizeable minority of medical advisors recommend annual inactivated flu vaccines for patients taking efalizumab. The benefits and risks of vaccination in patients treated with efalizumab have not been established.

in Table II. Because evidence-based data are lacking and because there is no correct monitoring and vaccination protocol that applies to every patient, we only offer our consensus statement recommendations as a rough guide for physicians to consider. These are summarized in Table III.

In reviewing the data available to help us decide which tests to consider in patients treated with

biologics and which vaccinations to administer, it is clear that long-term follow-up of large numbers of patients in well-monitored registries will be essential if we are to develop meaningful guidelines that protect our patients against the complications of these therapies. It has also become clear that these drugs have been subjected to much closer scrutiny than any prior therapies, with double-blind,

placebo-controlled trials in more than 1000 patients for each drug. Many of the potential complications of biologics are also recognized in patients treated with methotrexate or cyclosporine even though those treatments were never subjected to such close scrutiny. As noted above, there have been cases of reactivation of TB in patients treated with methotrexate and with cyclosporine. Elevations of liver function test results are well recognized in patients treated with methotrexate and with cyclosporine and death or pancytopenia are recognized complications of methotrexate, even though large double-blind, placebo-controlled trials were never performed with this drug for psoriasis.

The monitoring that should be done with biologics is evolving as new information becomes available about these drugs. Any recommendations made here will have to be updated frequently as new developments necessitate changes.

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