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Long-term efficacy of biologics in dermatology

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Abstract

Chronic dermatologic diseases affect millions of people. The long-term nature of these diseases creates psychological and financial burden as well as substantially impacts patients' quality of life. Biologics, including adalimumab, etanercept, alefacept, efalizumab, and infliximab, are the newest therapeutic agents in the treatment of moderate-to-severe psoriasis and psoriatic arthritis and have been used in a variety of other dermatologic diseases. These agents act relatively quickly and effectively in 12-week clinical trials. Because these agents are used to treat patients for longer than 12 weeks, there is a need to review the safety and efficacy of these agents over longer periods of time. Many levels of evidence are available for biologics including high level of evidence from large, randomized, double-blind, placebo-controlled clinical studies. This review focuses on the available data for efficacy and safety for greater than 24 weeks of therapy. The studies supporting the use of rituximab and intravenous immunoglobulin in autoimmune blistering diseases are also presented in this review.

Keywords

biologics; long-term efficacy; safety

Introduction

Long-term therapy is often required for the treatment of dermatologic diseases because of their often chronic nature. This article reviews the long-term data for the efficacy and safety of biologic therapies including etanercept, adalimumab, alefacept, efalizumab, infliximab, rituximab, and intravenous immunoglobulin (IVIG). Many of these therapies have been evaluated in patients with psoriasis and psoriatic arthritis; however, there are also small amounts of data for other dermatologic diseases including, but not limited to, pyoderma gangrenosum, pemphigus, vasculitis, and hidradenitis suppurativa (HS). The majority of early clinical trials on biologics in psoriasis have demonstrated efficacy and safety limited to 12 weeks. This review will focus on the available data for safety and efficacy for 24 weeks and beyond. For most of the biologics, the psoriasis clinical trial data show efficacy at 24-plus weeks with little increase in serious adverse events. With this said, the studies have limitations in terms of the number of patients in each trial and the selection of patients followed long term. Additionally, serious, long-term events such as cancers may not occur until years after administering such medications.

Adalimumab

Adalimumab is a fully human monoclonal immunoglobulin G1 (IG1) antibody that neutralizes tumor necrosis factor (TNF) by blocking its interaction with p55 and p75 cell surface TNF receptors, and by modulating biological responses that are induced or regulated by TNF.

Adalimumab and psoriasis

Adalimumab has been evaluated for up to 120 weeks in psoriatic arthritis and 60 weeks in psoriasis. Forty milligram dosing weekly and every other week has been shown to be well tolerated and has long-term effectiveness (defined here as effectiveness after approximately 2 years treatment) in patients with moderate-to-severe psoriasis. Patients followed for 1–2 years did not show increased rates of adverse events compared to patients at 12 weeks. The main limitation of the adalimumab studies is the selection of patients enrolled in the extension studies. Importantly, the patients in the extension portion of the study were on the whole early responders who chose or were chosen to continue in the study. Nonetheless, within this population, the data suggest patients who respond by 12 weeks with Psoriasis Area Severity Index (PASI) 75 are more likely to continue to respond. As will be discussed below, there is a suggestion that adalimumab may need to be taken continuously. Patients who achieved PASI 75 scores on adalimumab who were then re-randomized to placebo were unable to maintain these scores. There are three main studies that address long-term efficacy and they are detailed below.

The first is a multicenter, randomized, double-blind, placebo-controlled study of 147 patients with chronic plaque psoriasis receiving adalimumab (40 mg every other week (eow) or 40 mg/week) that showed 53% of patients taking adalimumab every other week, 80% of the patients taking it weekly and 4% of control achieved PASI 75 response at 12 weeks. At Week 24, 56% of patients receiving 40 mg eow and 64% of those receiving weekly dosing continued to show PASI 75 responsiveness (1). At Week 60, 56% of 40 mg eow dosing and 64% of 40 mg weekly dosing continued to show PASI 75 response suggesting the efficacy is maintained. The medication was generally well tolerated with 9% of patients discontinuing therapy secondary to an adverse event. The most frequently reported side effects were nasopharyngitis and upper respiratory infection. Fourteen patients experienced a serious adverse event during the 60-week period (3 receiving every other week and 11 receiving weekly treatment). The events included malignant melanoma (two patients), squamous cell carcinoma with lymphadenopathy (one patient), cerebrovascular events (two patients), breast carcinoma (one patient), gastric adenocarcinoma (one patient), coccidiomycosis (one patient), tuberculosis (two patients – reactivation latent tuberculosis (TB) and one conversion), osteoarthritis, kidney stones, and coronary artery disease.

The second long-term trial evaluated the efficacy over a 52-week period. In this multicenter trial, 1212 patients were randomized to 40 mg adalimumab every other week or placebo for the first 15 weeks. The trial was then converted to an open-label trial (2). Once again, there is selection bias as patients with a PASI of 75 from either treatment arm in the initial period were enrolled in the long-term study (580 adalimumab arm and 26 placebo arm). Patients who achieved PASI 75 at Week 15 were eligible to continue through Week 33, and those with PASI 75 at Week 33 were eligible to continue to Week 52. At 16 weeks, 70% of patients receiving adalimumab achieved a PASI 75 compared to 7% of controls. At 52 weeks, 70% of patients receiving adalimumab continued to achieve PASI 75. Adalimumab may not be effective unless it is continuously given as patients who achieved a PASI 75 at 33 weeks on adalimumab but were then re-randomized to placebo lost adequate response by 52 weeks. Less than 2% of patients discontinued the trial primarily because of adverse events. There was no difference in adverse events with longer trial period. Infections were the most common serious infection (cellulitis and abscessed most common). Non-melanoma skin cancer (six patients) also

occurred. There were no cases of lymphoma, demyelinating syndrome, or lupus. There was a single case of tuberculosis.

Adalimumab and psoriatic arthritis

The third study evaluates long-term efficacy in psoriatic arthritis over a 2-year period. The main limitation of the present study is that patients who were on non-steroidal anti-inflammatory agents (NSAIDs), other disease-modifying antirheumatic drugs (DMARDs), or prednisone at the start of the study could continue these medications throughout the study. A second limitation is that this group used PASI scores for only a subset of patients, used some physician global assessment (PGA) scores and primarily American College of Rheumatology (ACR) scores. This variability makes it difficult to directly compare the present study to the other large trials. In this double-blind placebo-controlled trial, patients ($n = 298$) completed a 24-week double-blind period and then 285 patients were enrolled in an open-label extension study receiving 40 mg adalimumab subcutaneous every other week for up to an additional 120 weeks (3). The mean duration of treatment was 100 weeks. Fifty-four patients were increased to 40 mg weekly during the study with 38 patients switched at 12 weeks due to failure to show >20% improvement in their joints. The study used ACR improvement scores and modified total Sharp score to evaluate treatment response. PASI was only used in patients with 3% body surface area (BSA) of skin disease. After 24 weeks, the mean change in modified total Sharp score was -0.2 for the adalimumab group ($n = 144$) and 1.0 for the placebo group ($n = 152$) showing improvement for the study group. Outcomes for ACR were also improved. Inhibition of radiographic progression and improvements in joint disease were maintained in most patients during long-term, open-label treatment. Greater than 20% achieved and maintained a PASI 100 ($n = 128$ at enrollment) at 48 weeks. A total of 56.6% had a PGA of clear or almost clear at 104 weeks. The safety profile during long-term treatment was consistent with safety data during short-term therapy. There was no indication of an increase in serious infection, malignancy, demyelination, congestive heart failure, and lupus-like syndrome.

Overall, adalimumab can be an effective and relatively safe long-term medication for psoriasis and psoriatic arthritis. The effectiveness may, however, decline if the medication is not used continuously as patients who achieved PASI 75 scores on adalimumab lost some efficacy within 12 weeks of being off the medication. If patients do not respond in the initial 12 weeks, it is unlikely that they will respond to this medication after this time period.

Alefacept

Alefacept is a recombinant fully human LFA-3-IgG1 fusion protein that binds to CD2 on T cells and functions to block CD2-LFA-3 co-stimulatory signal for CD45RO+ memory effector T cell activation. Alefacept also depletes the pool of activated T cells by enabling natural killer cells to bind to activated T cells. It is this T cell depleting activity that likely explains the reason that patients continue to experience clinical improvement after therapy has ended (4). This medication varies from other biologics in that it is a drug prescribed for intermittent therapy.

Alefacept in psoriasis

Alefacept has demonstrated long psoriasis remission times in patients treated for up to 60 weeks. In relevant studies, there were low incidences of malignancy, serious infection, hospitalization, or hypersensitivity reactions overall, and these incidences did not increase with subsequent 12-week courses. The main limitation of the alefacept data is that the number of patients evaluated at extended time periods is small, and one significant extension study assesses efficacy using PGA rather than PASI 75. This makes it more challenging to compare this trial to other trials that use PASI responses.

There are four relevant studies that assess long-term efficacy. The first is a Phase III study in which patients who achieved PASI 75 after a 12-week course of alefacept 15 mg per week ($n = 54$) were maintained on alefacept for 7 months. The study shows that all patients maintained at least a PASI 50 for this period of time; however, the group does not record PASI 75 scores at the subsequent time intervals (5). The second is an extension study for patients enrolled in alefacept intravenous (IV) or intramuscular (IM) Phase III trials. Here the efficacy data have been presented for up to 60 weeks of therapy. There are inherent problems in both design and selection with this extension study. The first is that the IV administration was recorded with PASI scores, but IM administration was recorded via PGA. As in adalimumab, patients were enrolled if they were considered responders in the initial 12 weeks of therapy. Most important, the number of patients drops from 521 to 39 at 60 weeks, and it is likely that responders have been positively selected in the present study, influencing the reported response of treatment. Still, among responders in the IV therapy group, PASI 75 response rates were increased from 29% at 12 weeks ($n = 521$) to 54% at 60 weeks ($n = 39$). The result of long-term use for IM therapy was evaluated by the PGA scale. PGA for IM administration increased from 21% classified as "clear or almost clear" during Course 1 ($n = 457$) to 41% during Course 4 ($n = 100$) but decreased during Course 5 to 30% ($n = 50$) (6,7). In the present study, there is a hint that there is loss of efficacy after four courses of therapy not only because the percent of people reaching PGA of "clear to almost clear" drops to 30%, but the number of participants drops to 50 from the initial 457. Information was not provided as to why the remaining 402 did not complete the study, making it difficult to interpret this data and raising questions about a possible loss of efficacy. A third, smaller randomized single center study compared the safety and efficacy in 16 weeks versus 12 weeks in 20 patients with chronic plaque psoriasis. This group demonstrated that those patients who received an additional four doses of alefacept showed a more durable response with a mean change in PASI score from baseline of 62% for patients receiving 16 weeks of continuous therapy versus 40% for those receiving 12 weeks.

In 2005, there was an integrated analysis of 1869 patients with chronic plaque psoriasis from 13 trials who received up to nine cycles of therapy over 5 years. The safety and tolerability of the therapy was addressed, and the most common side effects such as headache and upper respiratory infections were constant (8).

Overall, alefacept seems to be well tolerated in these longer-term studies. There may be a weak signal in this data that, after multiple cycles, the efficacy may decline. The precipitous drop in patient numbers in the extension phases of these studies may suggest that only a subpopulation responds well to this medication. This needs further investigation in larger series of patients.

Alefacept in psoriatic arthritis

A 24-week study of efficacy of the combination of alefacept and methotrexate was completed by Mease and colleagues (9). In this randomized, double-blind, placebo-controlled trial, patients ($n = 185$) received 15 mg of alefacept ($n = 123$) or placebo ($n = 62$) in combination with methotrexate for 12 weeks and then methotrexate alone for 12 weeks. Patients were eligible for enrollment if they had active psoriatic arthritis despite treatment with methotrexate for >3 months. Patients were followed for an additional 12 weeks. The end point was the proportion of patients achieving 20% improvement in the ACR criteria at 24 weeks. Five patients discontinued the trial (four in the alefacept group and one in the placebo group). Fifty-four percent of patients in the alefacept group reached an ACR20 response at 24 weeks compared to 23% of the placebo group. A significant reduction in tender joint count, tenderness, and swelling was noted in the alefacept group. Response rate at 14 weeks was similar to response rate at 24 weeks in the alefacept group. Radiographic progression was not studied. In the present study, alefacept appears to improve efficacy in patients already on methotrexate.

Alefacept in pyoderma gangrenosum

Alefacept has been used for other dermatologic diseases such as pyoderma gangrenosum. One is an open-label pilot study with four patients treated with IM alefacept for 20 weeks. After 20 weeks, the group was followed for an additional 12 weeks and improvement was shown in 25% of these patients by PGA (10). One patient had complete remission; two showed marked improvement, and one had slight improvement. Longer-term therapy and larger numbers of patients will be necessary to make statements about long-term efficacy and safety in this population of patients. Other case reports exist, but the data are weak.

Efalizumab

Efalizumab is a recombinant humanized monoclonal antibody against the alpha subunit (CD11a) of LFA-1, which modifies T cell activation and trafficking.

Efalizumab efficacy in psoriasis

Efalizumab has been evaluated for safety and efficacy for up to 36 months. The main limitation of these studies is that some of the patients received higher than Food and Drug Administration-approved doses of the medication. The second limitation is that in one large study, patients received concomitant ultraviolet B phototherapy or another systemic therapy. Together, these make it difficult to assess whether long-term efficacy is related to the phototherapy or high doses of this medication or another systemic medication. The safety profile was stable with long-term use.

Two trials evaluate the long-term efficacy and safety of this medication. The first is a Phase III trial that evaluates the efficacy and safety of efalizumab for 12 weeks ($n = 556$) plus a 12-week extension period ($n = 516$). Twenty-seven percent of patients achieved a PASI 75 at 12 weeks and 44% at 24 weeks. The common side effects such as headache, nausea, chills, fever, myalgia, and vomiting within 48 hours of administration declined in the second 12-week period, and there was no change in serious adverse events except for an increase in reports of arthritis (19 cases) in the second 12 weeks in the treatment group. Of patients reporting arthritis, only one achieved a PASI 75 response. The authors note 12/19 had a history of arthritis prior to the study. Still the increase in arthritis is a cause for concern as this medication may be used in patients with psoriatic arthritis. The authors do highlight that there was maintenance of the Dermatology Life Quality Index (DLQI) score from 12 weeks (DLQI = 5.6) to 24 weeks (DLQI = 5.9) overall (11).

A separate Phase III study evaluated 339 patients for 36 months of continuous therapy and reported their experiences in two different papers at 27 months and then at 36 months (12, 13). Patients received subcutaneous efalizumab (2 mg/kg/wk) for 12 weeks then converted to maintenance therapy (1 mg/kg/wk). Two hundred ninety entered the maintenance study phase and 170 patients received up to 27 months of therapy. The most frequent reason for discontinuation was the patient's decision ($n = 40$), adverse events ($n = 30$), investigator's decision ($n = 19$), and "lost to follow-up" ($n = 13$). Many of these patients also received concomitant therapy including ultraviolet B phototherapy ($n = 21$). Fifty-three patients received an excluded systemic therapy concomitant with efalizumab. Four percent of the patients received an escalated dose of 4 mg/kg/week after the initial dose of 2 mg/kg/week in the first 3 months. Both are higher than the standard 1 mg/kg/week dosing. The use of concomitant therapy and high doses of weekly medication makes it difficult to assess the role of efalizumab in maintaining PASI 75. Nonetheless, the PASI 75 at 12 weeks was 41% and 47% at 27 months in the efalizumab group. After 36 months ($n = 108$), continued improvement was observed. A total of 45.4% achieved PASI 75, respectively, compared to 41% at 12 weeks and 47% at 27 months (13). Efalizumab was generally well tolerated over 36 months of continuous therapy

with no increase in the overall incidence of adverse events, and no new common adverse events emerged. The occurrence of serious side effects including infection, psoriasis, and malignancy was stably low during the maintenance period. Psoriasis adverse events (sometimes known as rebound) such as pustular or erythrodermic psoriasis flares seemed to decrease over time in the present study. One patient was diagnosed with Stage I bulky small cell non-Hodgkin's lymphoma after completing 24 months of therapy. Non-melanoma skin cancers were the most common malignancy. Lymphoma was noted in two patients, gastrointestinal cancer in two patients, lung cancer in one patient, prostate cancer in one patient, and melanoma in situ in one patient.

In 2007, an Italian group reported their 2-year experience with 100 patients receiving efalizumab for plaque psoriasis. They showed that patients who responded in the initial 12 weeks had a 70% continued response in subsequent follow-up. Sixty-five percent achieved PASI 75 at 52 weeks ($n = 37$) and 67% at 100 weeks ($n = 9$) (14).

Long-term studies of efalizumab suggest that it is relatively safe up to 3 years and well tolerated. There are difficulties with interpreting the data secondary to the use of concurrent therapy. Nonetheless, in all trials, patients who respond at 12 weeks are most likely to continue to respond after extended therapy. One case of transverse myelitis was observed during the clinical development program (2762 efalizumab-treated patients) and neurologic events, including cases of Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, facial palsy, and transverse myelitis, have been observed in patients receiving efalizumab in the post-marketing setting (15). Caution should be exercised in patients who developed neurological symptoms on efalizumab. In October 2008, Genentech, Inc., the manufacturer of efalizumab, announced in a post-marketing study that a case of progressive multifocal leukoencephalopathy resulting from John Cunningham (JC) virus was identified in a 70-year-old patient who received efalizumab for more than 4 years for chronic plaque psoriasis (16).

Efalizumab and psoriatic arthritis

Efalizumab is not recommended for psoriatic arthritis. A Phase II randomized, double-blind, placebo-controlled multicenter study demonstrated that at 12 weeks, efalizumab was not effective in treating psoriatic arthritis; longer study has not been performed (17). In addition, two more recent reports suggest that efalizumab may potentially play a causal role in the development of psoriatic arthritis. Meyers et al. report on two patients who developed psoriatic arthritis while on longstanding efalizumab therapy for psoriasis (18). A retrospective review of multiple treatment centers also identified 16 cases of new-onset psoriatic arthritis (19). Interpretation of these newly described cases needs further study since the onset of psoriatic arthritis can often present after the diagnosis of psoriasis, and therefore at this time, a causal role cannot be concluded.

Efalizumab in lichen planus

There is limited data on other dermatologic diseases and long-term efficacy of efalizumab. There is one case report of a 29-year-old woman from Turkey who received 3 months of efalizumab for treatment of lichen planus. This patient had resolution of skin lesions and cessation of pruritus. The medication was tolerated well with some abdominal discomfort and fatigue, and the patient remained clear 12 weeks after stopping therapy (20).

Efalizumab in alopecia areata

Efalizumab was recently studied for the treatment of alopecia areata. In 2006, Kaelin et al. reported a single patient with alopecia universalis who was noted to have hair regrowth while on efalizumab (21). However, when 62 patients with alopecia areata were enrolled in a Phase

If placebo-controlled trial over a 6-month period, efalizumab was not found to be an effective therapy (22). Although the present study is small, it suggests that efalizumab is not an effective modality for this disease.

Etanercept

Etanercept is a dimeric fusion protein comprising the extracellular ligand-binding portion of the human p75 TNF receptor and the fragment crystallization (Fc) portion of human IgG1 that inhibits the activity of TNF-alpha.

Etanercept in psoriasis

There have been a number of Phase III trials with open-label extension analyzing varying doses of etanercept as well as continuous versus interrupted therapy in chronic plaque psoriasis. Etanercept has been evaluated for up to 144 weeks. Etanercept is well tolerated long term and appears to be efficacious in both children and adults. Event-associated reactions did not increase with increased weeks on treatment. All Phase III trials have demonstrated efficacy at 24 weeks and many more evaluate up to 48 weeks and beyond. As with the other biologics discussed above, the main limitation of all of these extension studies is that smaller pools of patients are eligible for the extension phases, and eligible patients for extended medication achieve PASI 75 during the first phase. This suggests the efficacy may not reflect the entire study population but a subpopulation of early responders.

Papp et al. reported that in patients who continued etanercept 25 mg two times a week, the percentage of patients who achieved PASI 75 at Week 48 was similar to Week 24 (23). There is a suggestion in the present study that decreasing patients from 50 mg two times a week after 24 weeks of therapy to 25 mg two times a week may decrease efficacy. There is another Phase III randomized, double-blind trial with an open-label extension for up to 144 weeks. In the present study, all patients received etanercept after 12 weeks ($n = 591$), and the data show that at 96 weeks, 51.6% of the original placebo group and 51.1% of the original etanercept group had achieved PASI 75 (24). This result was maintained until 144 weeks (25). There were two deaths that occurred during the study. One died of cardiac arrest 11 months into treatment, and the second died of presumed myocardial infarction 10 months after the start of therapy. Nine malignancies and 14 non-melanoma skin cancers were reported in this 96-week trial (26).

One double-blind study does compare dosing of etanercept over a 24-week period. In the present study ($n = 672$), patients received low dose (25 mg once a week), medium dose (25 mg two times a week), or high dose (50 mg two times a week). At 12 weeks, 4% of placebo, 14% of low dose, 34% of medium dose, and 49% of the high-dose group achieved PASI 75. At 24 weeks, 25% of the low dose, 44% of the medium dose, and 59% of the high-dose group achieved PASI 75. These changes were mirrored by improvement in the PGA. The patients in the higher-dose group did not show an increase in serious adverse events (27).

Evaluation of a randomized open-label trial of continuous 50 mg twice weekly versus interrupted therapy (50 mg once weekly) also showed that whereas the proportion of responders in continuous versus interrupted groups were similar at 12 weeks, continuous therapy patients showed a higher percentage of responders at 24 weeks (PASI 75 71% vs. 59.5% continuous versus interrupted therapy) (28).

Combining therapy may increase long-term efficacy and may decrease dosing frequency. One 24-week randomized control trial evaluated combining etanercept (25 mg two times a week or 25 mg once a week) and acitretin (0.4 mg/kg daily) in the therapy of chronic plaque psoriasis ($n = 60$) (29). At Week 24, PASI 75 response was achieved by 10 of 22 patients in the etanercept group (45%), 6/20 in the acitretin group (30%), and 8/18 (44%) in the group treated with

etanercept plus acitretin. The authors concluded that combined etanercept (25 mg once weekly) and acitretin (daily) was as effective as etanercept 25 mg two times a week.

Together these studies suggest etanercept is a relatively safe long-term treatment for psoriasis. Combined therapy and continuous therapy may be required to maintain maximum efficacy. Both 25 mg two times a week and 50 mg two times a week were shown to be effective, though one study shows that decreasing dosing from 50 mg twice weekly to 25 mg twice weekly may lead to a reduction in efficacy.

Etanercept and psoriatic arthritis

Whereas there are no studies that compare the long-term efficacy and safety of etanercept in psoriasis versus psoriatic arthritis, there are two studies that show long-term efficacy in the psoriatic arthritis population. The most significant is a 2-year study (30). Two hundred five patients were randomized to placebo or etanercept (25 mg two times weekly) for 24 weeks, and then 169 patients entered the open-label phase (48 weeks of etanercept 25 mg two times a week). One hundred forty-four patients of the original 169 were evaluated for radiographic progression for up to 2 years. One challenge of interpreting this data is that the patients were allowed to take concomitant methotrexate, corticosteroids or NSAID, and dose modifications of these medications were permitted during the maintenance phase. PASI 50 ($n = 102$) and Psoriatic Arthritis Response Criteria were met by 62 and 84% of etanercept–etanercept patients at the end of 48 weeks. PASI 75 was met and maintained by 36% of the patients at the end of 48 weeks. Radiographic progression (measured at 6, 12, and 24 months) was inhibited in etanercept patients at 48 weeks. The group reports that the medication and extended exposure were well tolerated with overall similar rates of adverse events but does not provide specific details of adverse events. The second is a smaller open-label study where a group of 10 patients with severe psoriatic arthritis resistant to DMARDs was treated with 25 mg etanercept two times a week and was followed for 26 months. Half of the patients ($n = 4$) took concomitant cyclosporine or prednisone. At the end of 26 months, eight patients completed the study and four patients had no swollen or tender joints, and mean PGA decreased and was maintained for an average of 26 months (31).

Etanercept appears relatively safe for psoriatic arthritis. The interpretation of both studies, however, is limited by the concomitant other systemic medications.

Etanercept and long-term efficacy in children

Unique to etanercept is a study that has addressed long-term efficacy (defined here as 48 weeks) in children 3–17 years of age. This is a 48-week study in children and adolescents with plaque psoriasis ($n = 211$). These patients were initially randomized to a double-blind trial of 12 weeks of once weekly subcutaneous injections of placebo or 0.8 mg of etanercept/kg of body weight (maximum of 50 mg), followed by 24 weeks of once weekly open-label etanercept. Patients were then re-randomized at 36 weeks to placebo or etanercept (32). At 12 weeks, 57% of patients receiving etanercept achieved PASI 75 (compared to 11% of placebo). At 36 weeks, rates of PASI 75 were 68% for patients initially assigned to etanercept. During withdrawal period, 42% of those who were re-randomized to placebo lost response. As in adults, this suggests that continuous therapy is required for maintenance of response. During the trial period, four serious adverse events occurred including three infections and one ovarian cyst.

Etanercept and HS

Aside from psoriasis and psoriatic arthritis, there are few studies that address the long-term efficacy of etanercept in patients with other chronic dermatologic diseases. There is a recent open-label Phase II study of etanercept in 10 patients with severe hidradenitis (33). In the present study, patients were administered subcutaneous doses 50 mg once weekly for 12 weeks

and then were followed up to 24 weeks using the Sartorius score and the visual analog scale (VAS). There was >50% score improvement in six patients at Week 12 and in seven patients at Week 24. The VAS was decreased compared to baseline in seven patients at Week 12 and in six patients at Week 24. Treatment was well tolerated by all patients with no reported adverse reactions, and all patients reported a decrease of local pain at the site of lesions after Week 4. Previously, Cusack and Buckley reported six patients with severe HS treated with etanercept (25 mg subcutaneously twice weekly for 24 weeks) (34). There was a reduction in the self-reported disease activity and in DLQI scores. At 24 weeks, the mean reduction for self-reported disease activity was 24% and DLQI was 64%. There is another case report of the long-term efficacy of etanercept in HS (35). In this case report, a 32-year-old man with a 6-year history of severe hidradenitis was treated with 50 mg etanercept subcutaneously twice a week for 24 weeks, followed by a dose reduction to 25 mg twice weekly for 24 weeks. Treatment was well tolerated and a sustained improvement was noted after 4 weeks. Although these data are promising for efficacy in hidradenitis, a double-blind, placebo-controlled trial is required to fully understand the role etanercept may play in the long-term treatment of HS.

Etanercept and hepatitis C

In 2004, Magliocco and Gottlieb reported three cases of patients with worsening psoriasis while on antiviral therapy for hepatitis C who tolerated etanercept therapy without any worsening of their viral titres (36). Since that time, two other cases have been reported of patients with both psoriasis and hepatitis C where long-term etanercept therapy (1 year) was administered without worsening of viral titres during the treatment course (37).

Infliximab

Infliximab is a chimeric monoclonal antibody that consists of a murine fragment antigen binding (Fab) portion specific for human TNF-alpha and the constant region (Fc) of human IgG1. It binds with high specificity and affinity to free and membrane-bound TNF-alpha.

There is limited data on the long-term efficacy of infliximab in dermatologic disease. In the available studies, infliximab is well tolerated and there are no increased adverse events at long time points. There are two trials addressing the role of infliximab for long-term efficacy in psoriasis, two in psoriatic arthritis, one for atopic dermatitis, and two for hidradenitis. Whereas the psoriasis and psoriatic arthritis studies are relatively large, the studies in atopic dermatitis and hidradenitis have less than or equal to 10 patients each. Nonetheless in these studies, infliximab is well tolerated and appears efficacious in the psoriasis and psoriatic studies, for only 2/9 atopic dermatitis participants and in the short term for patients with hidradenitis. The studies are outlined below.

Infliximab long-term efficacy in psoriasis

In one study, infliximab has been evaluated for 52 weeks in patients with moderate-to-severe psoriasis. The present study evaluated continuous versus intermittent infliximab regimens (38). Eight hundred thirty-five patients were randomized to induction therapy with infliximab 3 mg/kg ($n = 313$) or 5 mg/kg ($n = 314$) or placebo ($n = 208$). Infliximab-treated patients ($n = 595$) were then randomized again at Week 14 to continuous or intermittent maintenance regimens at their induction dose. Two hundred fifty-two patients discontinued the study before Week 50. During the first 14 weeks, approximately 20 patients from each group (placebo, infliximab 3 mg/kg, and infliximab 5 mg/kg) discontinued the trial. Between Weeks 14 and 50, an additional 162 patients discontinued the trial. Fewer patients in the 3 mg/kg completed the study treatment when compared to the other treatment groups, and more patients in the intermittent group dropped out overall. The demographics as well as the severity of the disease was similar among all groups. The onset of clinical effect was rapid with many patients in both

dose groups achieving PASI 75 as early as 2 weeks. Among the 10-week PASI 75 responders, response was better maintained by the infliximab-every-8-week maintenance group compared with the as-needed group. The median percent improvement in PASI 75 through Week 50 was 89.6% in the 5 mg/kg every-8-week group and 80.6% in the 3 mg/kg every-8-week group compared with 76.4% and 72.4% in the as-needed groups, respectively. The number and type of adverse reactions was stable up to 50 weeks with only increased infusion reactions in patients receiving intermittent therapy. Twelve cases of malignancies were reported including 1 breast cancer, 1 squamous cell cancer, 9 basal cell cancers, and 1 adenocarcinoma. Two cases of tuberculosis were reported. Lupus-like syndrome was reported in two patients.

The second psoriasis trial included 378 patients in a multicenter, double-blind, placebo-controlled study. Here again patients were treated with infliximab with the standard induction protocol followed by infusions every 8 weeks. At Week 24, patients previously receiving placebo were rolled into an active treatment group. PASI 75 at Weeks 10 and 24 was 80 and 82%, respectively. However, at Week 50, PASI 75 had decreased to 61%, thereby suggesting that some patients are not able to maintain effectiveness long term (39).

Infliximab and psoriatic arthritis

Infliximab has also been studied in psoriatic arthritis long term. The first study looked at its efficacy after 50 weeks in 104 patients (40). This same group of patients was then followed for a total of 2 years (41). ACR20 was achieved by 62% of patients at Week 98. Sixty-four percent of patients who met the criteria of skin involvement demonstrated a PASI 75. In addition, joint progression based on radiographic progression was inhibited as well throughout this period, thereby demonstrating sustained joint and skin improvements.

Infliximab in atopic dermatitis

Infliximab has also been evaluated in a 46-week long-term study of moderate-to-severe atopic dermatitis (42). In this small investigator-initiated open prospective pilot study, nine patients were enrolled and infliximab was administered at 0, 2, 6, 14, 22, 30, and 38 weeks. Improvement was monitored based on the Eczema Area and Severity Index, Pruritus Severity Assessment, and DLQI. Reduction of the Eczema Area and Severity Index score by 50% was considered excellent, 30–49% moderate, and <29% nonsignificant. At 2 weeks, there was significant improvement in all patients. At 10, 14, and 30 weeks, six patients were withdrawn due to nonsignificant response, and one patient withdrew due to a serious infusion site reaction. At 46 weeks, only two patients, both excellent responders, remained in the trial. Pruritus Severity Assessment did improve for the two remaining patients.

Infliximab and HS

Long-term efficacy has also been evaluated in HS. In one investigator-initiated study, 10 patients were treated with 5 mg/kg of infliximab at 0, 2, and 6 weeks and were followed for 1 year. The disease was measured using acne score and DLQI. All patients improved within 2–6 weeks. The average acne score diminished from 164 to 89 after 1 year. The mean DLQI was reduced from 18.4 to 9.3 after 1 year. Three patients had no evidence of recurrence after 2 years, the others relapsed within a mean of 8.5 months. The present study does not provide evidence of long-term efficacy with maintenance therapy. Side effects included respiratory infections, nausea, cough, and abdominal pain. A Phase II open-label study was recently reported (33). In the present study, 10 patients were treated with 5 mg/kg once weekly for 12 weeks and then were followed for 24 weeks using a VAS and Sartorius score. A >50% score improvement was found in six patients at Week 12 and in seven patients at Week 24. The treatment was well tolerated. It is unclear whether infliximab demonstrates long-term efficacy in hidradenitis. As with etanercept, larger, double-blind, placebo-controlled studies are required to evaluate long-term efficacy.

IVIG

IV administration of exogenous pooled human immunoglobulin (IVIG) has been used for several decades to treat such disorders as primary immunodeficiency, hypogammaglobulinemia, and idiopathic thrombocytopenia (43). It is currently not approved for any dermatologic disease. Nonetheless, off-label use in dermatology, such as in Stevens–Johnson syndrome (SJS), pemphigus vulgaris, bullous pemphigoid, and vasculitis, has suggested some potential for this modality. This is little to no long-term data on IVIG in dermatologic disease likely because many of the disorders treated are rare. Most of the evidence comes from retrospective reviews with a heterogeneous number of IVIG cycles and doses of IVIG per cycle. The best evidence for long-term efficacy comes from IVIG use in pemphigus, vasculitis, pyoderma gangrenosum, and bullous pemphigoid.

IVIG and vasculitis

In vasculitis, there is a small amount of data to show long-term efficacy. A multicenter prospective, open-label study of 22 patients showed that IVIG administered for 6 months to treat relapses of Wegner's granulomatosis or microscopic polyangitis induced remission in 13/22 patients at 9 months (44). All patients had an initial response to IVIG, but at 9 months, one had partial remission; seven relapsed, and one had treatment failure. In the 8/24 patients with remission, the response persisted at 24 months. This therapy had a good safety profile. Moderate and transient adverse effects included nausea during infusion, headaches at first infusion, and influenza-like symptoms at infusion. No severe or life-threatening events were reported.

There are additional case reports of IVIG being clinically beneficial in Churg–Strauss syndrome, polyarteritis nodosum, Behçet's, and leukocytoclastic vasculitis (43). None of these studies show long-term efficacy, however.

IVIG and pyoderma gangrenosum

IVIG has also been used to treat pyoderma gangrenosum. In one retrospective review of 10 patients, 7/10 patients had clearance of lesions in the setting of IVIG, and 6 of these patients were maintained with repeat doses of IVIG up to 14 months (45).

IVIG and bullous disease

In bullous pemphigoid, there are reports of over 35 patients successfully treated with IVIG (43). In the only prospective study, 15 patients were evaluated (46). Cycles were administered every 4 weeks until all lesions had healed and then the infusion was spaced out gradually by adding two additional weeks between cycles. If relapse occurred, the IVIG dosing was increased to every 4 weeks until remission was achieved. The time to obtain clinical response ranged from 2 to 4 months and the duration of IVIG was 17.0–26.5 months. Patients had few minor adverse effects.

There is one retrospective analysis of clinical response to monthly IVIG for patients with pemphigus vulgaris (10), pemphigus foliaceus (2), mucous membrane pemphigoid (4) epidermolysis bullosa acquisita (2), and linear IgA bullous dermatosis (1) (47). The number of cycles varied from 5 to 22. Only 4/19 cases had complete remission and 5 patients did not respond to therapy. The treatment was well tolerated with only one severe adverse effect, a deep venous thrombosis in a patient with a coagulation disturbance.

IVIG and other dermatologic disease

IVIG has been used in a wide variety of chronic dermatologic diseases and in the treatment of severe hypersensitivity reactions.

There is a retrospective review that evaluates 63 cases of immunoglobulin used to treat recalcitrant suppurative diseases such as hidradenitis, folliculitis decalvans, and chronic recurrent folliculitis (48). These patients were treated with IM immunoglobulin once a month for anywhere from 1 to 15 months depending on their response to therapy. Fifty-nine percent of patients showed overall improvement (global improvement scores) and were rated as “excellent response” or “good response” by the attending physician. Patients had periods without new lesions that ranged from 1 to 12 months following therapy.

In one report of 10 patients with chronic urticaria treated with IVIG (2 g/kg) daily for 5 days, 9/10 patients achieved remission and 3/10 maintained 3-year remissions (49).

In dermatomyositis, a random double-blind study evaluated the efficacy of IVIG and found it to be beneficial (50). However, the benefits of IVIG were of a small duration with effects averaging 6 weeks. Most of the original patients from the present study were then followed for 10 years and most continue to receive IVIG and respond to a variable degree. It is reported that some patients require more frequent infusions every 3–4 weeks to maintain excellent response. Others continue to improve on every 4- to 6-week regimens, but the authors suggest that the improvement is not as impressive as initially (51).

IVIG in SJS and toxic epidermal necrolysis (TEN)

In drug-induced disorders like SJS and TEN, 70% of case reports conclude that TEN patients benefit from IVIG (44). A few open-label prospective studies show mixed results. In one study, survival was correlated with relatively high doses of IVIG and when IVIG was started (52). In another prospective open-label study, no benefit was found for IVIG (53). Although none of these studies address long-term efficacy, SJS and TEN are not chronic diseases.

IVIG has mixed responses in dermatologic disease and evidence for long-term efficacy is sparse. The most promising data come from evaluation of IVIG in vasculitis, bullous pemphigoid, and pyoderma gangrenosum. Even in these diseases, the quality of the data is low, secondary to small numbers and design.

Rituximab

Rituximab is a monoclonal humanized antibody directed against the B cell-specific antigen CD20.

As with IVIG, there are no randomized double-blind studies of rituximab in dermatologic disease. Nonetheless, rituximab has been used in more than one million patients with CD20-positive non-Hodgkin's lymphoma, and severe side effects were only rarely observed (54). To date, rituximab has been used in a variety of blistering diseases. In autoimmune blistering patients, clinical remission has been induced in the majority of patients who receive rituximab; however, serious side effects were considerably higher compared with both patients with non-Hodgkin's lymphoma or non-bullous autoimmune disorders. In systemic lupus, dose escalation studies revealed no differences with respect to B cell depletion and clinical outcome in patients who received either a single infusion of 100 mg/m², a single infusion of 375 mg/m², or four weekly infusions of 375 mg/m² (55). Likewise, data on rheumatoid arthritis showed no difference in efficacy between two or four doses of 375 mg/m² (56).

For patients with blistering disease, most patients receive the lymphoma dosing schedule, which is 375 mg/m² for four infusions. There is a report of 11 refractory pemphigus patients who received three infusions of rituximab 375 mg/m² weekly, which was followed by rituximab every 4 weeks for another 4 months (57). Of the 11 patients, 9 had rapid resolution

of lesions and a clinical remission lasting 22–37 months. No side effects including infections were observed.

Schmidt et al. reviewed case reports of patients with autoimmune blistering diseases treated with rituximab (56). He found 54 patients, 39 with pemphigus vulgaris (PV), 6 with paraneoplastic pemphigus, 4 with bullous pemphigoid, 2 with pemphigus foliaceus, 2 with epidermolysis bullosa, and 1 with mucous membrane pemphigoid. Within this group of patients, most patients responded within the first 3 months. Follow-up periods ranged from 2 to 37 months with a mean of 11.5 months. Serious adverse events included two cases of fatal bacterial sepsis in one patient with paraneoplastic pemphigus and one with bullous pemphigoid, bacterial sepsis, bacterial pneumonia, and deep venous thrombosis.

A more recent report of IVIG use in pemphigus vulgaris evaluated two patients with recalcitrant PV treated with two courses of four weekly IV infusions of rituximab (375 mg/m²) with a 6-month follow-up interval. In these patients, clinical improvement was noted between 3 and 6 weeks after the first infusion. After the second course, complete remission was achieved. The patients were in full remission 6 months after the last rituximab infusion (58).

Rituximab appears to be effective in patients with autoimmune blistering disorders at doses and frequencies used in lymphoma patients. There is a suggestion that autoimmune blistering disorder patients are more likely to suffer from serious adverse events than lymphoma patients.

Conclusion

Biologic therapies for dermatologic indications have been evaluated up to 144 weeks. Although there are mixed levels of evidence for long-term efficacy of biologic medications, these medications appear to be safe and effective long term in patients with psoriasis. The data for other dermatologic diseases are more mixed with some patients not responding at all to some biologic treatment. Encouragingly, there are no more serious adverse effects reported with longer extension studies. Still, the most alarming events such as lymphomas and other cancers may not be detected until after the studies are completed or many years after the start of therapy. These medications can be cautiously used long term.

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