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REVIEW

A Delphi Consensus Approach to Challenging Case Scenarios in Moderate-to-Severe Psoriasis: Part 2

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ABSTRACT

Introduction: Clinicians may be confronted with difficult-to-treat psoriasis cases for which there are scant data to rely upon for guidance. To assist in managing such patients, who are typically excluded from clinical trials, a consensus panel of 14 experts in the field of psoriasis was formed to conduct a Delphi method exercise.

Methods: The exercise consisted of both survey questionnaires and a live meeting to review and

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discuss current data (as of 2009, when the exercise was conducted) and arrive at a consensus for optimal treatment options. Seventy difficult treatment scenarios were identified, and the top 24 were selected for discussion at the live meeting.

Results: Five of the 24 discussed case scenarios are presented in this article: (1) moderate-to-severe psoriasis that has failed to respond to all currently approved therapies for psoriasis; (2) palmoplantar psoriasis that is unresponsive to topical therapy and phototherapy; (3) erythrodermic psoriasis; (4) pustular psoriasis; and (5) the preferred therapeutic choice to combine with low-dose methotrexate. A previous article (part 1) presented six other scenarios.

Conclusion: The Delphi exercise resulted in guidelines for practicing physicians to utilize when confronted with patients with challenging cases of psoriasis.

Keywords: Acitretin; Biologics; Erythrodermic psoriasis; Palmoplantar psoriasis; Psoriasis; Pustular psoriasis; Methotrexate; TNF-α inhibitor

INTRODUCTION

Psoriasis is a difficult condition to treat, and it is often accompanied by comorbidities that confound diagnosis and complicate management. The literature on such scenarios is sparse, as patients with unusual or complex disease and comorbidities are typically excluded from clinical trials.

A consensus panel of 14 experts in the field of psoriasis was formed to conduct a Delphi method exercise to identify challenging clinical scenarios and to rank treatment approaches, in an effort to provide guidance to the practicing clinician.

Part 1 in this series presented six scenarios from this Delphi exercise: (1) psoriasis and human papilloma virus (HPV)-induced cervical or anogenital dysplasia; (2) concomitant psoriasis and systemic lupus erythematosus; (3) severe psoriatic nail disease causing functional or emotional impairment; (4) psoriasis therapies that potentially reduce cardiovascular morbidity and mortality; (5) older patients (≥65 years of age) with psoriasis; and (6) severe scalp psoriasis that is unresponsive to topical therapy [1].

The current paper presents five additional scenarios of interest to the practicing dermatologist: (1) moderate-to-severe psoriasis that has failed to respond to all currently approved therapies for psoriasis; (2) palmoplantar psoriasis (PPP) that is unresponsive to topical therapy and phototherapy; (3) erythrodermic psoriasis; (4) pustular psoriasis; and (5) the preferred therapeutic choice to combine with low-dose methotrexate. These selected scenarios were chosen by the first author (B.E.S.).

THE DELPHI METHOD

The Delphi method is particularly well suited for addressing healthcare-related issues because the outcome represents the collective judgment of the panel of experts on selected topics. The Delphi method includes three basic

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characteristics: (1) repeated individual questioning of the experts; (2) the avoidance of direct confrontation among the experts (e.g., anonymity); and (3) interspersed controlled opinion and feedback. Importantly, the Delphi method seeks to achieve consensus on complex scenarios where rigorous data are lacking. Available data on a given topic are reviewed extensively, presented, and discussed amongst the panelists. More importantly, by employing only anonymous voting by the panelists, the Delphi method settles controversy by eliminating the effects of either reputation or "personality." Consequently, anonymous voting after thorough review of the data allows the panelists to vote for what they truly believe, thus avoiding "groupthink" and sentiment guided more by "eminence," charisma, and dogmatism.

What follows is an application of the Delphi method for difficult-to-treat clinical scenarios in patients with moderate-to-severe psoriasis. This process occurred in the following three steps over approximately 5 months: (1) selection of difficult-to-treat psoriasis clinical scenarios; (2) selection of potential psoriasis treatment modalities; and (3) the matching, through systematic, iterative rounds of voting, of the clinical scenarios with the most appropriate treatments based on informed assessment of the peer-reviewed literature. At all times, the votes of the individual panelists were kept anonymous; thus, at no point was a single individual able to direct the outcome of any aspect of this process.

Method Overview

The employed Delphi exercise process is described in full in Part 1 of this study [1]. In brief, it began with the identification of 14 psoriasis experts from the United States (US). Individually, the panelists were asked to list challenging clinical scenarios and therapeutic options for psoriasis. The clinical scenarios were then selected and ranked, and the treatment options were listed. Twenty-four of the top-ranked scenarios were discussed during a live meeting and the treatment choices for each were voted on and ranked.

Classification of Experimental Evidence Supporting a Therapeutic Option

Recommendations from the Agency for Health Care Policy Research (AHCPR) were used to grade the experimental evidence as it relates to therapeutic recommendations in each case study. The categories of evidence include: level 1a: evidence from meta-analysis of randomized controlled trials (RCTs); level 1b: evidence from one or more RCT; level 2a: evidence from one or more controlled trials (without randomization); level 2b: evidence obtained through other well-designed studies (quasi-experimental); level 3: evidence from nonexperimental studies (descriptive studies such as comparative or correlation studies, or case–control studies); level 4: expert committee opinions, clinical experience.

Preliminary recommendations for treatments were made using the best available evidence extracted from published literature. The strengths of recommendations were graded as follows: grade A: category 1 evidence; grade B: category 2 evidence or extrapolation from category 1 evidence; grade C: category 3 evidence or extrapolation from category 1 or category 2 evidence; grade D: category 4 evidence or extrapolation from category 2 or category 3 evidence.

Where definitive scientific evidence was lacking, "expert opinion" and consensus (e.g., the community standard) were used for suggested recommendations for key practical issues.

RESULTS

Case Scenario 1. Moderate-to-Severe Psoriasis that has Failed to Respond to all Currently Approved Therapies for Psoriasis (all TNF Inhibitors, T-Cell Inhibiting Agents, and Acitretin) in Patients who Cannot Receive (a) Methotrexate, due to Excessive (>10 Drinks per Week) Alcohol Use; and (b) Cyclosporine, due to Either Unmanageable Hypertension or Significantly Reduced Kidney Function

Patients with severely recalcitrant psoriasis represent a subset of patients with comorbidities that exclude both methotrexate and cyclosporine use, but have also had no response to other options for moderate-to-severe psoriasis such as tumor necrosis factor alpha (TNF-α)-inhibitors, retinoids, and T-cell inhibiting agents. Currently, the data for these patients are sparse and there is frequent off-label use.

Ustekinumab, an inhibitor of interleukin (IL) 12 and 23, presents a unique therapeutic pathway in patients who are resistant to other therapies. Ustekinumab demonstrates strong efficacy data in moderate-to-severe psoriasis (grade A evidence) [2]. Up to 67% of patients achieved a Psoriasis Area and Severity Index (PASI) score of 75 by week 12 and over 90% reached a PASI 50 by week 28. This high response rate was seen in a group of patients where over 50% had been previously treated with a biologic agent and over 55% with a conventional systemic agent such as methotrexate, cyclosporine, acitretin, or psoralen ultraviolet A (PUVA) [2]. Among the ustekinumab partial responders, those achieving between a PASI 50 and 75 at 28 weeks, 51.9% had a prior inadequate response to a systemic or biologic agent, indicating particularly recalcitrant disease. However, increasing the dose to 90 mg and shortening the dosing interval to 8 weeks enhanced the response and allowed more patients to reach a PASI 75 [2].

Phototherapy using broadband or narrowband ultraviolet B (UVB) therapy or PUVA is another option for these patients. In one study, narrowband UVB was superior to broadband with a higher clearance rate, faster response time, and, consequently, fewer total treatments (grade B evidence) [3]. Despite a difference in clearance rate, broadband UVB was still able to clear 73% of treated lesions. In a separate study, PUVA had even greater efficacy, with an 84% clearance rate as compared to 65% with narrowband UVB (grade A evidence) [4]. At 6 months after their initial clearance, significantly more PUVA subjects retained their results, while more narrowband UVB subjects relapsed. On the negative side, studies show that PUVA also markedly increased the risk for nonmelanoma skin carcinoma and, possibly, malignant melanoma (grade C evidence) [5].

Combinations of phototherapy with other agents have been reported, allowing it to be an adjuvant to any of the prior failed monotherapy options. Acitretin and UVB therapy have greater efficacy than UVB therapy alone (grade A evidence) [6]. The acitretin and PUVA combination also has a higher clearance rate than PUVA alone and has the additional benefit of reducing the total PUVA exposure by 42% (grade A evidence) [7]. One study focused on the treatment of patients who were refractory to monotherapy with either narrowband or broadband UVB therapy, monotherapy with acitretin, or the combination of acitretin with broadband UVB. The most successful approach in these patients was a combination of acitretin

with narrowband UVB, which resulted in 72.5% of patients reaching a PASI 75 (grade C evidence) [8].

UV light has been combined with a few biologics, notably etanercept and alefacept. In a study of etanercept and narrowband UVB therapy, 85% of patients reached a PASI 75 after 12 weeks (grade C evidence) [9]. However, there were no monotherapy data for comparison, and general expectations would be a 73% clearance rate from UVB therapy alone [3]. Using a split-body study, alefacept was able to reduce PASI scores by 62%, and the addition of narrowband UVB therapy reduced the scores by 81% (grade A evidence) [10]. However, when the combination was compared to narrowband UVB therapy alone in a separate study, no significant difference was detected in patient response (grade A evidence) [11].

Some other therapeutic options include abatacept and 6-thioguanine, which are more commonly utilized in rheumatoid arthritis (RA). An initial trial of abatacept for psoriasis revealed a dose-dependent response and resulted in 46% of patients achieving a PASI 50 (grade A evidence) [12]. This improvement was seen in a population previously resistant to methotrexate, cyclosporine, phototherapy, or systemic corticosteroids. In addition, clinical improvement correlated with histological changes and reductions in T-cell activation (grade C evidence) [13]. While abatacept presents a new option for recalcitrant psoriasis, there currently is a lack of placebo-controlled studies and the optimal dose and dosing interval are unknown. In the RA population, there is an increased risk of serious infections and a higher rate of adverse events in patients with chronic obstructive pulmonary disease (COPD), and a requirement for ongoing monitoring for the risk of lung carcinoma and lymphoma (grade D evidence) [14]. For 6-thioguanine, there has been a high success rate, with 78% of patients clearing the majority, or all, of their lesions (grade C evidence) [15, 16]. Over 50% of the patients were able to maintain their results for 2 years. Despite the drug's efficacy, 35.5% of patients discontinued the therapy due to intolerable side effects. The most frequent toxicity from daily dosing is myelosuppression, found in up to 46.9% of patients. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels also may increase, although these elevations do not correlate with chronic liver disease. Pulse dosing has similar efficacy to daily dosing, but may lower the risk of adverse events (grade B evidence) [17].

In small clinical trials, mycophenolate mofetil reduced mean severity scores by 56% as compared with 9% for placebo (grade A evidence) [18, 19]. Over the course of treatment, significant improvement was noticeable by 6 weeks and 61% of treated patients reached a PASI 50 by week 12 (grade B evidence) [20]. Mycophenolate mofetil was also well tolerated with mild gastrointestinal effects, but the risk of leucopenia and the complications of immunosuppression remain (grade C evidence) [21].

Topical therapies may also have a role in recalcitrant psoriasis. A once-daily application of calcipotriene combined with corticosteroids was found to induce a 72% reduction in PASI scores by week 4, which is a higher efficacy than seen with biologic agents (grade C evidence) [22]. However, with severe disease encompassing a large body surface area, there may arise significantly increased cost, poor patient adherence, potential hypothalamus-pituitary axis suppression, and the cutaneous side effects of topical corticosteroids (grade B evidence) [23].

Discussion

The panelists agreed that patients with severely recalcitrant disease present a significant therapeutic challenge. Many of the participants suggested combining therapies, and, particularly, supplementing with UVB therapy or topical regimens. Azathioprine was mentioned as a potential therapy, given that 6-thioguanine is one of its metabolic products. The use of intramuscular corticosteroids was not discussed, but might remain an option for some patients who have a lessened risk for the possible adverse effects of that approach.

The top-ranked treatments for recalcitrant psoriasis include ustekinumab, narrowband UVB therapy, UV therapy + acitretin, broadband UVB therapy, PUVA, UV therapy + a biologic agent, 6-thioguanine, mycophenolate mofetil, abatacept, and topical steroids + calcipotriene. Figure 1 presents the final results of the voting by the panel on this topic. Since this Delphi Exercise was conducted ustekinumab has received approval from the US Food and Drug Administration for the treatment of moderate-to-severe psoriasis.

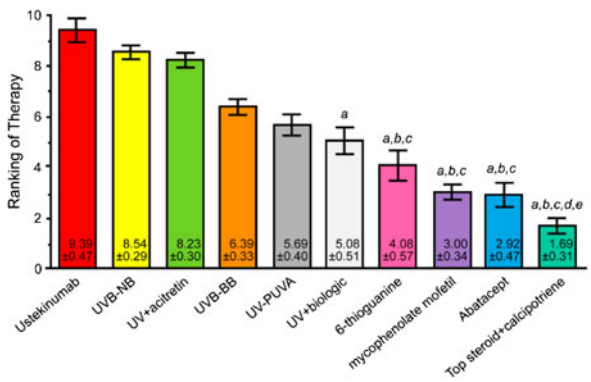

Fig. 1 Final results of the voting on case scenario 1, moderate-to-severe psoriasis that has failed to respond to all currently approved therapies for psoriasis. *a* denotes $P < 0.05$ compared with ustekinumab therapy; *b* denotes $P < 0.01$ compared with UVB-NB therapy; *c* denotes $P < 0.05$ compared with UV + acitretin therapy; *d* denotes $P < 0.01$ compared with UVB-BB therapy; *e* denotes $P < 0.05$ compared with UV-PUVA therapy. *PUVA* psoralen + ultraviolet A therapy, *UV* ultraviolet therapy, *UVB-BB* broadband ultraviolet B therapy, *UVB-NB* narrowband ultraviolet B therapy

Treatment Challenges: None.

Case Scenario 2. PPP that is Unresponsive to Topical Therapy and Phototherapy

While there are few data on the overall prevalence of PPP, approximately 17% of patients with psoriasis have palmar or plantar involvement (grade C evidence) [24]. Conversely, in those with PPP, a range of 2–24% will have evidence of psoriasis elsewhere [25]. However, the demographics differ in PPP from typical psoriasis, with a much higher incidence in women and a strong association to smoking (grade C evidence) [26]. Patients with palmoplantar involvement also experience higher rates of physical discomfort and disability (grade C evidence) [27].

The treatment of PPP is often challenging and may require systemic medications. A Cochrane analysis found evidence supporting the use of systemic retinoids, as the improvement rate difference over placebo was 44% and the ability to maintain clinical remission was much higher in the retinoid treatment group (grade A evidence) [28]. While the majority of studies were with etretinate, which is no longer available in the US, the analysis found that etretinate and acitretin did not differ in efficacy. PUVA shared a similar improvement rate difference of 44% above placebo. However, a combination of etretinate and oral PUVA surpassed the individual monotherapy results. The clearance rate for oral PUVA-etretinate reached 71%, compared to 35% with oral PUVA alone or 20% with etretinate alone. Low-dose cyclosporine, short-course tetracycline, and Grenz ray (low voltage X-ray therapy) were

found to improve PPP, but were unable to clear the disease. For topical therapies, the use of topical steroids under hydrocolloid occlusion was beneficial in inducing remission [28].

Several case reports suggest that the TNF-α inhibitors may be a viable therapeutic choice for PPP (grade D evidence) [29–32]. The various TNF-α inhibitors may be used in sequence with each other or in combination with acitretin (grade D evidence) [32, 33]. However, all three TNF-α agents, when used for the treatment of nonpsoriatic diseases, such as inflammatory bowel disease and RA, have documented incidences of inducing or exacerbating paradoxical psoriasis, with PPP representing up to 40.5% of these cases. This appears to be a class effect, as switching to a different TNF-α agent rarely results in a resolution of the issue. The addition of topical corticosteroids may assist in the control of this condition, while the discontinuation of the TNF-α inhibitor with the start of another systemic, non-TNF-inhibiting agent may lead to the highest resolution rate (grade D evidence) [34].

Discussion

For PPP, some panelists shared their success with topical PUVA and cyclosporine (as monotherapy), but noted that higher doses of cyclosporine may be required. Others referred to the increased association of PPP with smoking, suggesting that cessation could be important, although the data supporting this contention are not derived from rigorous studies. Some also supported the use of acitretin by itself or as an adjunct to an existing inadequate treatment. In regard to biologic agents, a few panelists shared anecdotal successes with infliximab.

The discussion also addressed the classification of PPP as a form of psoriasis. Some suggested that PPP may be a different entity than plaque psoriasis. The TNF-α inhibitor-induced psoriasis was also suggested to be a separate subset of disease due to its paradoxical induction and its relative recalcitrance to treatment.

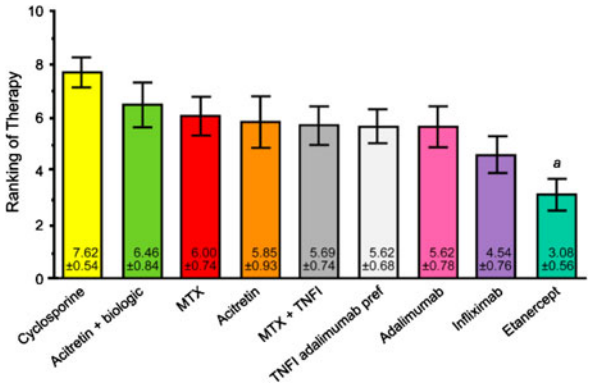

Fig. 2 Final results of the voting on case scenario 2, palmoplantar psoriasis that is unresponsive to topical therapy and phototherapy. *a* denotes $P < 0.01$ compared with cyclosporine therapy. *MTX* methotrexate, *pref* preferred, *TNFI* tumor necrosis factor inhibitor

The top-ranked treatments for PPP were cyclosporine, acitretin + a biologic agent, methotrexate, acitretin alone, methotrexate + a TNF-α inhibitor, TNF-α inhibitor (adalimumab preferred), adalimumab, infliximab, and etanercept. Figure 2 presents the final voting on PPP treatments.

Treatment Challenges: None.

Case Scenario 3. Erythrodermic Psoriasis

Hebra initially described erythroderma in 1868 as an exfoliative dermatitis involving more than 90% of the body surface, but today's definition remains nebulous as there are numerous etiologies for erythroderma. While the differential diagnosis may include systemic diseases, such as leukemia and lymphoma, a systemic drug reaction, or a paraneoplastic presentation of underlying cancer, the majority of cases arise from pre-existing skin

disease (grade C evidence) [35, 36]. Psoriasis may represent up to 40% of those cases [37]. Those with erythroderma also face a higher mortality rate than age-matched controls, and patients with psoriasis may be specifically at risk for staphylococcal septicemia (grade D evidence) [37].

Currently, there is a paucity of data to guide treatment, as erythrodermic psoriasis is almost always an exclusionary criterion in clinical trials. In a group of 33 patients, however, cyclosporine led to complete disease remission in 67% after 3 months and an overall response rate of 94% (grade B evidence) [38]. There are other also case reports supporting the efficacy of cyclosporine as a monotherapy and in combination with acitretin (grade D evidence) [39–41]. Monotherapy with both etretinate (grade A evidence) [42] and acitretin (grade C evidence) [43] demonstrated efficacy, although erythroderma was reported as a complication of acitretin use (grade D evidence) [44].

For the TNF-α inhibitors, there are cases of successful therapy with infliximab alone (grade D evidence) [45–48] and one case responding to a combination with cyclosporine (grade D evidence) [49]. There are no data for the use of methotrexate as monotherapy, although success with methotrexate in combination with etretinate has been reported (grade D evidence) [50]. Both adalimumab and etanercept have reports of success (grade B evidence) [51, 52]. While etanercept may take up to 24 weeks for substantial improvement, six out of 10 patients achieved a PASI 75 response.

Discussion

During the discussion of this case, panelists highlighted the differences in erythrodermic presentation. While in some cases it may be quite acute, other scenarios display a slow onset with a chronic clinical picture. With its rapid onset of action, cyclosporine was mentioned as the favored therapeutic agent for acute cases. However, if there is a delayed response to cyclosporine, then other etiologies should be considered. Aside from systemic agents, some panelists shared good results with the use of inpatient care and topical steroids. They noted that the practicality of an inpatient approach must be considered on a case-by-case basis. While etanercept was not specifically listed among the voting choices, panelists recommended that it be considered in clinical practice as there are data supporting its use.

The top-ranked treatments for erythrodermic psoriasis were cyclosporine, infliximab, methotrexate + a TNF-α inhibitor, a TNF-α inhibitor (infliximab preferred), adalimumab, a TNF-α inhibitor (adalimumab preferred), methotrexate alone, methotrexate + cyclosporine, ustekinumab, and acitretin. Figure 3 presents the results of the final voting on this issue.

Treatment Challenges: None.

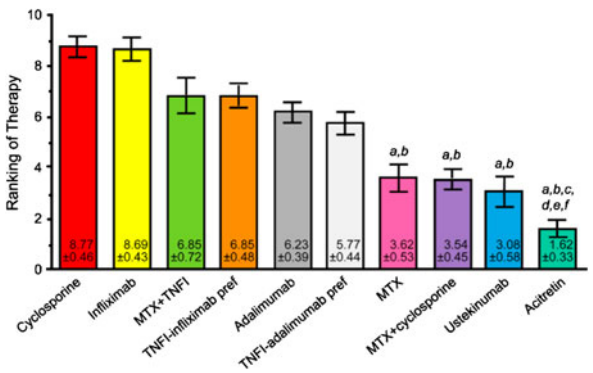

Fig. 3 Final results of the voting on case scenario 3, erythrodermic psoriasis. *a* denotes $P < 0.01$ compared with MTX therapy; *b* denotes $P < 0.01$ compared with infliximab therapy; *c* denotes $P < 0.01$ compared with MTX–TNFI therapy; *d* denotes $P < 0.01$ compared with TNFI–infliximab preferred therapy; *e* denotes $P < 0.01$ compared with adalimumab therapy; *f* denotes $P < 0.05$ compared with TNFI–adalumumab preferred therapy. *MTX* methotrexate, *pref* preferred, *TNFI* tumor necrosis factor inhibitor

Case Scenario 4. Pustular Psoriasis

In general, pustular psoriasis may be categorized by distribution. The generalized form may be Von Zumbusch psoriasis, an annular subtype, or the pustular psoriasis of pregnancy known as impetigo herpetiformis. The localized variants include PPP and acrodermatitis continua. The impact on patients may range from pain and disability to life-threatening states. The etiology of pustular psoriasis includes infection, drugs, or the withdrawal of steroids. Identification of the cause is fundamental, as resolving the underlying disorder should be the first intervention. For psoriasis-specific therapy, the rapidity of the response, the ability to maintain the response, and the safety of the agent must all be considered. For generalized pustular psoriasis, there are no RCTs and the majority of clinical evidence derives from case reports.

Cyclosporine has been efficacious for generalized pustular psoriasis in its juvenile form [53], in pregnancy [54], and in adults (grade D evidence) [55, 56]. It has a rapid onset of action. The major toxicity is from dose-dependent renal damage, occurring mostly with high-dose or long-term treatment (grade A evidence) [57]. Accordingly, most recommendations are to limit cyclosporine exposure to 1–2 years, and some cases require a transition medicine for further treatment (grade D evidence) [58].

In the prevention of recurrent pustules, acitretin has been shown to be effective (grade D evidence) [59, 60]. Etretinate has evidence for moderate improvement to complete clearance in generalized pustular psoriasis, but is no longer commercially available (grade A evidence) [42]. Acitretin has shown efficacy in children as young as 2.5 months (grade D evidence) and in adults, with visible results in fewer than 10 days (grade C evidence) [37, 59]. A recent study from France found that acitretin was the first-line treatment in 89% of cases (grade C evidence) [60]. Combining acitretin with narrowband UVB phototherapy may be synergistic, and has demonstrated efficacy for pustular psoriasis in childhood (grade D evidence) [61, 62]. Narrowband UVB therapy, with or without topical corticosteroids, is of particular use during pregnancy, when many therapeutic options have unknown teratogenic risks (grade D evidence) [63].

Methotrexate effectively treats pustular psoriasis in children (grade B evidence) [64] and adults (grade C evidence) [65–67]. The successful combination of methotrexate and cyclosporine for severe pustular psoriasis associated with psoriatic arthritis has also been reported (grade B evidence) [68, 69]. For the arthritis component, the combination may reduce joint inflammation, but does not alter pain levels and overall quality of life (grade A evidence) [70]. Because cyclosporine and methotrexate are associated with potential renal and hepatic damage, respectively, some have discouraged the combination due to concerns of additive toxicity (grade D evidence) [71], but dose reduction of the two individual drugs when used together may reduce risk.

A study from Japan found that retinoids had the highest success rate at 84.1%, followed by methotrexate (76.2%), cyclosporine (71.2%), PUVA (45.7%), and tonsillectomy for those with recurrent streptococcal pharyngitis (16.7%) (grade C evidence) [67]. Systemic corticosteroids were also found to be efficacious when used only in the presence of severe systemic symptoms.

Of the TNF-α inhibitors, infliximab, etanercept, and adalimumab have evidence of efficacy. Infliximab has demonstrated both

immediate responsiveness and long-term tolerability, often in combination with methotrexate (grade D evidence) [72–74]. There is also evidence that infliximab is beneficial for the articular disease that may be seen with pustular psoriasis (grade D evidence) [75]. Infliximab has a rapid onset of action, as normalization of vital signs and laboratory findings may be seen within 24 h of the first infusion and pustules may resolve within 24–48 h (grade D evidence) [76, 77]. Sequential therapy with infliximab for an immediate response followed by etanercept for long-term therapy has been reported (grade D evidence) [78]. Etanercept has been successful as a monotherapy in treating generalized pustular psoriasis, including in those who are unresponsive to infliximab (grade D evidence) [79]. Etanercept taken 50 mg twice weekly led to significant reductions in the PASI scores of patients. The PASI scores were stably maintained over 48 weeks, even following a reduction to weekly 50 mg dosing at 24 weeks. Adalimumab has shown efficacy in adolescence and adulthood through 72 weeks of treatment (grade D evidence) [80–82].

Patients with pustular psoriasis who are also positive for the human immunodeficiency virus (HIV) present a unique therapeutic challenge, as HIV infection is known to exacerbate psoriasis and these patients are sensitive to immunosuppression and opportunistic infection. While there are reports concerning the use of TNF-α inhibitors in patients with either pustular psoriasis or HIV existing separately, there is currently only one report of etanercept success in a patient with both conditions concomitantly (grade D evidence) [83]. In this, case success was maintained over a 20 week period and was not associated with any infections requiring antibiotic treatment.

Discussion

Fortunately, generalized pustular psoriasis is a rare entity. Some panelists shared their approach of treating with a medicine that is fast and useful in the short term, followed by a transition to a longer-term medication. Others stated that they preferred to use one agent, such as infliximab, throughout therapy. One panelist pointed out that some patients will have complete resolution of their disease after the initial treatment, while a subset will have recurrences.

In discussing the option of transitioning from one TNF-α inhibitor to another, such as infliximab to etanercept as described above, the group agreed that this approach is not commonly done. Some warned that infliximab has been shown to sometimes have a loss of efficacy with intermittent use, so that if the transition is made, the drug might no longer be an option for further use if needed later.

Overall, the majority of the panel considered cyclosporine as their first-line agent, both for its ease of prescription and rapid onset of action. Others favored infliximab as the first-line treatment. Acitretin was questioned in this setting, as its onset of action would be slower than other agents that were mentioned, but it remained an option given its recognized efficacy.

The top-ranked treatments for this condition were cyclosporine, infliximab, a TNF-α inhibitor (infliximab preferred), methotrexate + a TNF-α inhibitor, methotrexate alone, acitretin + a biologic agent, acitretin alone, methotrexate + cyclosporine, and UV phototherapy + acitretin. Figure 4 presents the final results of voting by the panels about treatments for pustular psoriasis.

Treatment Challenges: None.

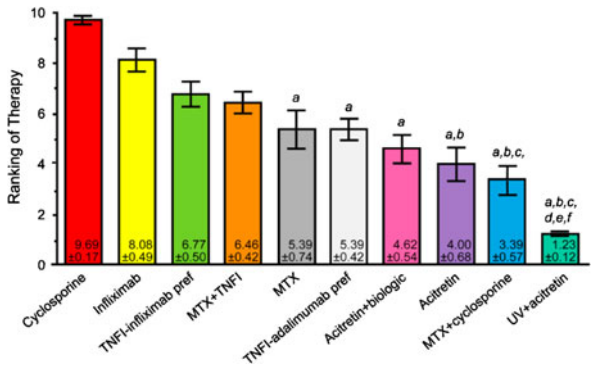

Fig. 4 Final results of the voting on case scenario 4, pustular psoriasis. *a* denotes $P < 0.05$ compared with cyclosporine therapy; *b* denotes $P < 0.05$ compared with infliximab therapy; *c* denotes $P < 0.01$ compared with TNFI–infliximab preferred therapy; *d* denotes $P < 0.01$ compared with MTX–TNFI therapy; *e* denotes $P < 0.05$ compared with MTX therapy; *f* denotes $P < 0.05$ compared with TNFI–adalumumab preferred therapy. *MTX* methotrexate, *pref* preferred, *TNFI* tumor necrosis factor inhibitor, *UV* ultraviolet therapy

Case Scenario 5. The Preferred Therapeutic Choice to Combine with Low-Dose Methotrexate

In psoriasis, methotrexate has many clinical advantages. For patient safety, methotrexate has a long clinical record and well-known and uncommon side effects that may be partially preventable. For patient health, methotrexate demonstrates good efficacy for the skin and joints, no evidence of tachyphylaxis, and the ability to reduce systemic inflammation and the potentially associated cardiovascular risks. Methotrexate is also widely available at a low cost, allowing access for many patients. In addition, methotrexate is often a component of combination therapies. This discussion assessed the preferential therapeutic choices for combination with methotrexate in treating psoriasis.

The efficacy of methotrexate as a monotherapy in psoriasis has been documented over a 16 week period. Of those treated with methotrexate, 35.5% achieved a 75% reduction in the PASI score and 7.3% attained complete clearance of their skin disease (PASI 100), as compared with 18.9 and 1.9% among placebo-treated patients, respectively (grade A evidence) [84]. However, combination therapies have been primarily examined in patients with RA, and rarely in psoriasis or psoriatic arthritis.

In RA, the addition of a TNF-α inhibitor to methotrexate has demonstrated superior efficacy to methotrexate monotherapy; the improvements were similar among all of the available TNF-α inhibitors (grade A evidence) [85]. The combination of etanercept and methotrexate enabled a significantly higher proportion of patients to reach the American College of Rheumatology (ACR) criteria of 20, 50, or 70 reduction in tender or swollen joints, and overall disease remission (grade A evidence) [86]. At 2 years, 48.5% of patients on the combination therapy were still at ACR 70, while etanercept alone maintained only 27.4% at ACR 70 and methotrexate alone had 20.6%. The addition of adalimumab to long-term methotrexate therapy has been shown to have similar effects on the ACR scores of patients over a 24 week period (grade A evidence) [87, 88]. These patients also maintained their initial 6 month response rate through a follow-up period of 4 years (grade A evidence) [89]. In methotrexate-naive patients [90] or patients with an inadequate response to methotrexate [91], this combination had the capacity to slow radiographic progression of the disease (grade A evidence). Infliximab trials also supported improved response rates in combination therapy as an ACR 50 was found in 31% of patients compared with 5% from methotrexate alone (grade A evidence) [92]. A separate study with methotrexate-naive subjects analyzed response rates and systemic inflammatory

markers from high-dose methotrexate with or without infliximab (grade A evidence) [93]. While methotrexate was able to improve disease control, it did not prevent radiographic deterioration of joints in those with high baseline levels of pre-existing joint disease and those with high systemic inflammation evident from CRP and erythrocyte sedimentation rate (ESR) levels. However, the combination of methotrexate and infliximab was successful in inhibiting joint disease progression in this subset of patients.

There is emerging evidence that early, aggressive intervention with combination therapies may be best for long-term outcomes in patients with RA. The success with methotrexate monotherapy was similar in early (diagnosed within the past 2 years) or established RA, but the combination therapy with adalimumab was significantly more effective in achieving ACR 70 levels in early RA, with 41% of early RA subjects responding, compared with 18% of established RA subjects (grade A evidence) [91].

In contrast to RA, the literature on psoriasis or psoriatic arthritis is sparse. In patients with plaque psoriasis who responded inadequately to methotrexate as monotherapy, after the addition of etanercept, significantly more patients were at "clear" to "almost clear" in the Physician's Global Assessment (PGA), and almost twice as many patients achieved PASI 75. Importantly, there was less of a response in those in whom methotrexate was tapered after the addition of etanercept (grade B evidence) [94]. Adalimumab was shown to improve ACR and PASI scores when used with methotrexate, but this was only statistically significant for PASI 50 (grade A evidence) [95]. Alefacept and methotrexate have been successful in the treatment of psoriasis, with 53% of patients on the combination therapy reaching PASI 50, a significant increase from 17% with methotrexate monotherapy (grade A evidence) [96]. For the psoriatic arthritis component, methotrexate alone only reached an ACR 20 response in 17% of patients, while the combination with alefacept achieved the response in 54%. An open-label extension of this study demonstrated that patients might benefit from a second course of alefacept, supplementing a stable methotrexate dose, as more patients reached ACR 50 and ACR 70 with the repeated combination (grade B evidence) [97].

Discussion

Overall, the panelists emphasized the lack of psoriasis-specific data for agents to combine with methotrexate and noted that most of the evidence and conclusions available are based on extrapolations from the RA data. In addition, while combination therapies may be effective, they each have their own set of individual risk profiles and patient comorbidities that may limit therapeutic options.

The combination of cyclosporine and methotrexate was suggested with great trepidation. Initial data suggested utility in the control of skin and joint disease at lower doses in combination than either would require as a monotherapy. However, renal toxicity, which is not reversible with cyclosporine taper, was detected on long-term combination treatment (grade B evidence) [69]. In a separate study of patients with plaque, pustular, or erythrodermic psoriasis, with or without arthritis, the combination of cyclosporine and methotrexate reduced PASI scores by a median of 77.4%, but also induced a proportion of patients to develop altered renal or liver function (grade B evidence) [68]. Panelist opinion varied on this subject, with some using this combination frequently, others refusing to use the combination after

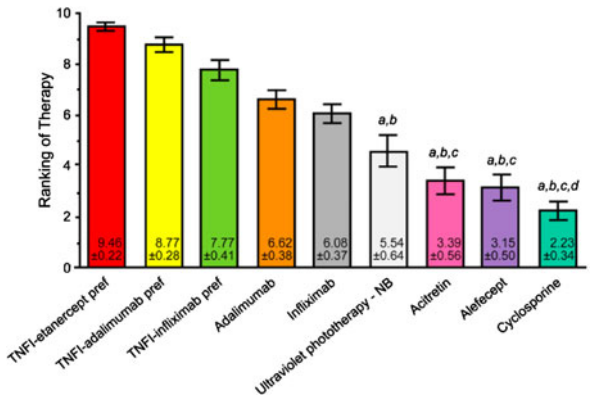

Fig. 5 Final results of the voting on case scenario 5, the preferred therapeutic choice for combination with methotrexate. *a* denotes $P < 0.01$ compared with TNFI–etanercept preferred therapy; *b* denotes $P < 0.05$ compared with TNFI–adalimumab preferred therapy; *c* denotes $P < 0.05$ compared with TNFI–infliximab preferred therapy; *d* denotes $P < 0.05$ compared with adalimumab therapy. *NB* narrowband, *pref* preferred, *TNFI* tumor necrosis factor inhibitor

experience with significant adverse events, and others replacing cyclosporine with biologic agents.

The top-ranked treatments for this case scenario were a TNF-α inhibitor (etanercept preferred), a TNF-α inhibitor (adalimumab preferred), a TNF-α inhibitor (infliximab preferred), adalimumab, infliximab, narrowband UV therapy, acitretin, alefacept, and cyclosporine. Figure 5 presents the results of the final round of voting.

Treatment Challenges: None.

DISCUSSION

This investigation further employs the Delphi process to determine acceptable treatment recommendations in difficult-to-treat psoriasis patients. An additional five case scenarios discussed at the live meeting are presented in this paper: moderate-to-severe psoriasis that has failed to respond to all currently approved therapies for psoriasis in patients who cannot receive methotrexate or cyclosporine; PPP that is unresponsive to topical therapy and phototherapy; erythrodermic psoriasis; pustular psoriasis; and the preferred therapeutic choice to combine with low-dose methotrexate. Six other cases were presented in a separate article [1].

As described previously, the iterative and anonymous voting process of the Delphi method depends on an unbiased view of the available clinical data and leads to more objective consensus. The final rankings should be viewed as guidance for practical, potentially effective, and likely safe treatment in a majority of instances. Because the Delphi method does not introduce better data for a given topic, it cannot produce an idealized outcome. The process we have utilized selects rational treatment choices for each clinical scenario, but these choices often are not supported by rigorous studies. Importantly, this evidence-based approach relying on anonymous opinion is a more objective tool for reaching consensus. The process has multiple limitations, all enumerated in Part 1 of this analysis [1]; however, the Delphi exercise helps clinicians in practice benefit from more objective consensus opinion, offering guidance during challenging clinical scenarios, and allowing for the use of specific treatment approaches that often are effective and safe.

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