Evidence-based recommendations for the management of acne fulminans and its variants

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Background: Acne fulminans (AF) is a severe variant of inflammatory acne. It typically manifests as an explosive worsening and ulceration of skin lesions, and can be associated with systemic symptoms. However, there is a paucity of evidence-based information and no clear guidelines concerning the classification and treatment of AF.

Objective: To better define the spectrum of AF and its variants, devise optimal therapeutic approaches, and identify areas of future research.

Methods: A panel of physicians with expertise in severe acne vulgaris was convened after a comprehensive literature review of severe acne variants. Priority topics were reviewed and presented by each panelist at a 5-hour conference. Following review of the audiotape and scribed notes from the conference, surveys were utilized to address points of controversy and to clarify consensus recommendations.

Results: Appropriate clinical case presentations and consensus survey questions were utilized to create final recommendations based on both the literature and the expert consensus.

Limitations: Limited evidenced-based data and prospective studies in the literature concerning the treatment of AF is available.

Conclusion: These guidelines better characterize AF and provide health care practitioners approaches to the classification, treatment, and prevention of AF and its variants. (J Am Acad Dermatol 2017;77:109-17.)

Key words: acne fulminans; diagnosis; isotretinoin; PAPA; PAPASH; pseudotumor cerebri syndrome; SAPHO; treatment.

Acne fulminans (AF) is an uncommon and incompletely understood severe variant of inflammatory acne. Its onset is often abrupt, with rapid development of painful erosions and hemorrhagic crusts that lead to severe and often disfiguring scars. In its most extreme form, this disorder can manifest as systemic inflammation, including fever, arthralgias, and osteolytic bony lesions, which occasionally necessitate hospitalization.

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The confusing terminology for this disorder, as well as its variable clinical and therapeutic characteristics, has contributed to a lack of well-defined treatment approaches. For this reason, a panel with expertise in the treatment of AF was convened to better define the spectrum of this disorder, devise optimal therapeutic approaches, and identify areas of future research. A thorough literature review and review of all available evidence was utilized to make recommendations.

CAPSULE SUMMARY

- Acne fulminans (AF) is an uncommon and incompletely understood severe variant of inflammatory acne.
- Evidence-based expert panel recommendations provide a more complete understanding of AF and its variants.
- These guidelines provide health care practitioners with approaches to the classification, prevention, and treatment of AF and its variants.

METHODS

Twelve physicians with extensive academic knowledge base and clinical expertise in severe acne vulgaris were selected by the chairs (Sheila Fallon Friedlander, MD, and Andrea L. Zaenglein, MD) to take part in developing a consensus of the pathogenesis, prevention, treatment, and future research directions of AF and its variants. The ultimate goal was to develop evidence and experience-based recommendations of care for these disorders.

Prior to convening, a comprehensive literature review was conducted of all forms of severe acne, and relevant articles were placed in a file-sharing program available to all participants. Nine priority topics were identified by the chairs and each topic was assigned to 1 or 2 panelists for a critical literature review and preparation of presentation summaries. All topic areas were presented and discussed by the full panel at a 5-hour conference, with audiotaping transcripts and scribed notes collected. Following review of these materials, the chairs engaged in 2 rounds of surveys to address points of controversy and to design and clarify consensus recommendations.

DEFINITIONS

AF was initially labeled acne maligna or acute febrile ulcerative acne conglobota. However, in 1975 Plewig and Kligman coined the term AF, emphasizing its distinctive characteristics. The spectrum of severity ranges from skin-limited disease (acne fulminans without systemic symptoms, AF-WOSS) to acne fulminans with systemic symptoms (AF-SS) (Fig 1, *A* and *B*). The common feature of all forms of AF consists of ulcerative lesions that preferentially occur on the trunk with hemorrhagic erosions and crusts that heal with severe scarring.

Isotretinoin therapy might trigger AF in patients with severe acne, particularly when treatment is initiated at high doses. This form of the disease does not usually have systemic symptoms (isotretinoin-induced AF without systemic symptoms, IIAF-WOSS) (Fig 1, *C-E*) but the ulcerations, crusting, and scarring are often severe. When systemic involvement is present, the proposed term is isotretinoin-induced AF with systemic symptoms (IIAF-SS).

The panel recommends the terminology and classification proposed in Table I. The group recognizes AF as a spectrum of disease with or without systemic symptoms, and with isotretinoin and other drug associated forms. These terms replace the previously used terms: "acne maligna," "acute febrile ulcerative acne conglobata," "pseudo-acne fulminans," and "acne fulminans sine fulminans." In addition, recommended examination and diagnostic studies are described in Table II.

INCIDENCE AND DEMOGRAPHICS

AF is rarely reported, with <200 cases documented in the literature.[1-3] The incidence of reports has decreased over the last decade, supporting the belief that severe disease with systemic findings might be decreasing.[2] Some have postulated that recognition of disease and treatment are now occurring earlier, and acne is therefore less likely to progress to a truly fulminant form.[2] The panel agreed that the de novo form of AF is quite uncommon. In contrast, IIAF-WOSS appears to be increasing in frequency, which is almost certainly related to more widespread use of isotretinoin.

AF typically presents in adolescent males between the ages of 13 and 22.[1,2,4] It is most common in Caucasians, while a less common and milder form has been reported in patients of East Asian descent.[2] In addition, patients who develop AF generally have a prior history of acne with a mean duration of 2 years.[1] Celtic origin has been suggested, but not confirmed as a risk factor. Other risk factors for AF include increased testosterone levels and the use of anabolic steroids.[5,6] AF has been reported with Marfan syndrome and late-onset congenital adrenal hyperplasia.[7,8] Genetics also plays a role, as identical

Abbreviations used:

AF:	acne fulminans
AF-SS:	acne fulminans with systemic symptoms
AF-WOSS:	acne fulminans without systemic symptoms
ICP:	intracranial pressure
IIAF-SS:	isotretinoin-induced acne fulminans with systemic symptoms
IIAF-WOSS:	isotretinoin-induced acne fulminans without systemic symptoms
IL-1:	interleukin 1
PAPA:	pyogenic arthritis, pyoderma gangrenosum, and acne
PAPASH:	pyogenic arthritis, pyoderma gangrenosum, acne, and hidranitis suppurative
PASH:	pyoderma gangrenosum, acne, and hidranitis suppurative
PTCS:	pseudotumor cerebri syndrome
SAPHO:	synovitis, acne, pustulosis, hyperostosis, and osteitis

twins and siblings with identical human leukocyte antigen phenotypes have been reported with similar presentations.[9,10] Identified risk factors for IIAF include higher initiating doses of isotretinoin and the presence of macrocomedones.[11]

ASSOCIATED DISORDERS: SAPHO, PAPA, PASH, AND PAPASH

SAPHO, PAPA, PASH, and PAPASH are syndromes that share the manifestations of joint disease and severe acne. SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a musculoskeletal disorder with variable skin findings.[12] Its most common skin manifestation is palmoplantar pustulosis. Acne, including acne conglobata, AF, and hidradenitis suppurativa, are less frequently associated with SAPHO. High fever and weight loss are also often present. The largest case series of SAPHO noted a preponderance of women and a mean age of 32 years; only 18% demonstrated severe acne.[13]

PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, and acne) is an exceedingly rare autosomal dominant disorder that presents in childhood with pauci-articular, nonaxial joint disease.[14,15] There is no sex preference. Joint disease is the predominant feature early in life with resolution in puberty when acne—usually severe—occurs. Lower extremity pyoderma gangrenosum lesions are variable in occurrence and severity.

The symptoms of PASH include pyoderma gangrenosum, acne, and hidranitis suppurative. PAPASH syndrome, in addition to the findings listed for PASH, is also associated with pyogenic arthritis. Mutations in the PSTPIP1 gene have been reported in both PAPA and PAPASH syndromes.[16]

PATHOGENESIS

The sequence of events leading to the explosive cutaneous inflammation in patients with AF is unknown. Alterations in innate immunity, autoimmunity, adaptive immunity, and autoinflammation have been proposed; however, the evidence is inconclusive.[17] An immunological deficiency or a generalized hypersensitivity state was suspected but no specific clues could be found in qualitative or quantitative immunoglobulin assays, skin tests, biopsies, or other studies.[17] The autoinflammatory syndromes are characterized by inflammasome activation leading to release of proinflammatory interleukin-1 (IL-1). *Propinobacterium acnes* activates inflammasomes in the skin leading to IL-1 release.[18] Therefore, studies examining IL-1 levels in AF lesions would be of interest.

Regarding a possible mechanism for IIAF, it appears that isotretinoin likely induces inflammation in the skin early in the treatment course of all treated individuals. The metabolic burst from peripheral blood neutrophils was significantly greater in patients receiving isotretinoin than in untreated acne patients or age-matched controls.[19] Isotretinoin significantly increases expression of genes in 2 ontogenies relating to innate immune activation.[20] Therefore, it is possible that the extent of inflammation induced by isotretinoin, or the patient's response to it, could account for the development of IIAF. Retinoids are also known to stimulate granulation tissue and enhance wound healing.[21] Excessive stimulation of granulation tissue can result in pyogenic granuloma formation, which has been associated with isotretinoin therapy.[22] In addition, numerous cytokines are present in sebocytes.[23] Acute apoptosis of large numbers of sebocytes with isotretinoin therapy likely results in the release of cytokines into the dermis leading to intensification of inflammation.

THERAPY

Corticosteroids and isotretinoin

Unfortunately, there is an absence of large-scale randomized controlled trials evaluating treatment for AF. Nonetheless, a review of case series, individual reports, and case analyses supports the use of systemic corticosteroids in combination with isotretinoin when treating all forms of AF.[1,4,11,24-27]

Systemic corticosteroids are recommended at the immediate onset of AF to quickly control the severity of inflammation.[1] The panel recommends initiating prednisone 0.5 mg/kg/day to 1 mg/kg/day

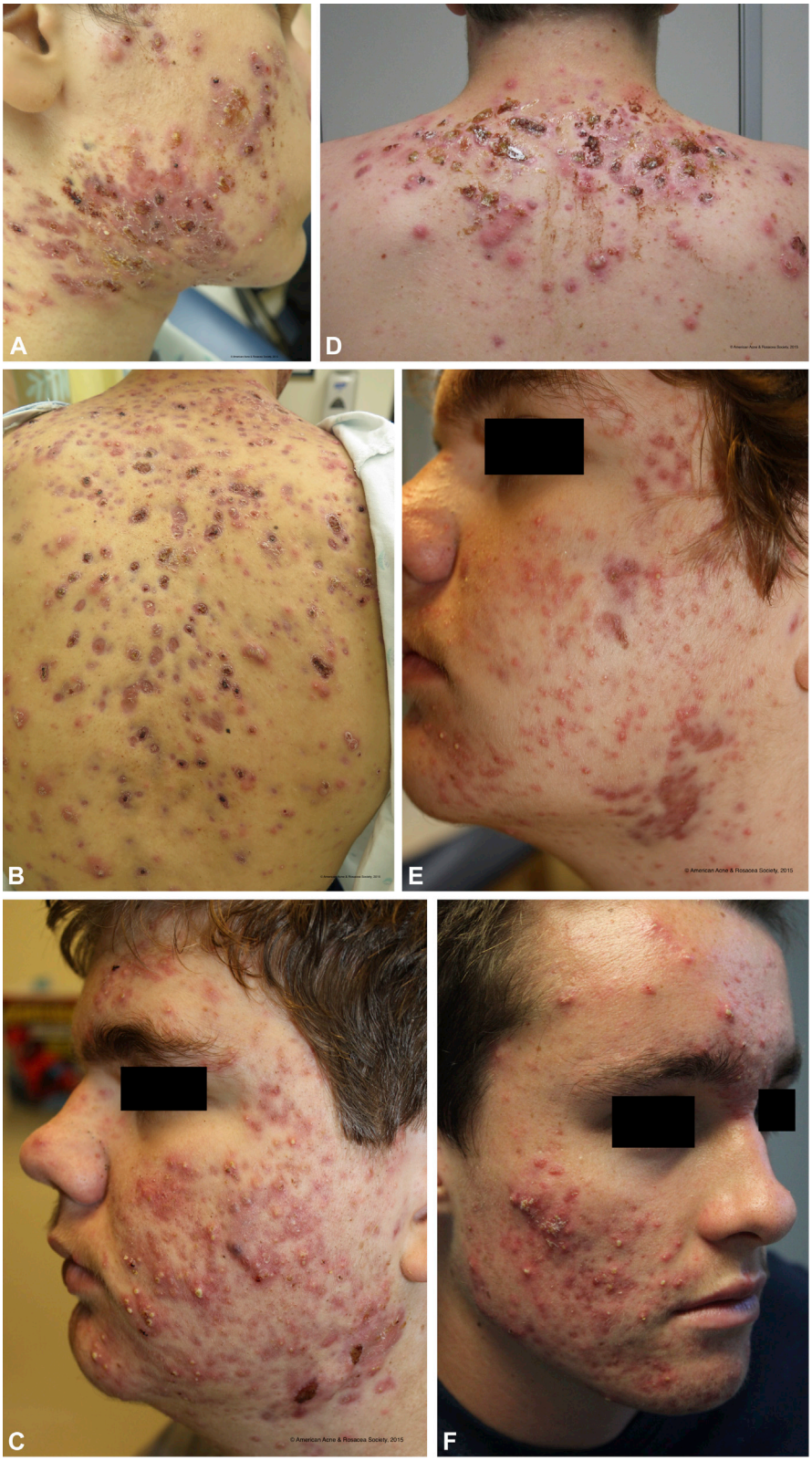

Fig 1. Representative patients with acne fulminans and their management. **A** and **B**, 14-year-old boy with papules, pustules, hemorrhagic crust, and scars on the face (**A**) and back (**B**). He did not have fever but did present with bone pain and leukocytosis (white blood cell count 18 cells/μL), thrombocytosis (468 platelets/μL), and elevated C-reactive protein (5.7 mg/L).

Table I. Terminology of acne fulminans

Term	Abbreviation	Definition
Acne fulminans with systemic symptoms	AF-SS	Abrupt, dramatic flare of inflammatory acne, with erosions +/− crusts, ulcers, hemorrhagic nodules/plaques, as well as systemic findings (fever, malaise, bone pain, arthralgias, erythema nodosum, and leukocytosis) Laboratory abnormalities might include anemia, leukocytosis, elevated erythrocyte sedimentation rate, and C-reactive protein X-ray findings: Osteolytic bony lesions; usual sites include sternum, clavicles, sacroiliac joints, hips
Acne fulminans without systemic symptoms	AF-WOSS	Abrupt, dramatic flare of inflammatory acne, with erosions +/− crusts, ulcers, and hemorrhagic nodules/plaques without systemic findings
Isotretinoin-induced acne fulminans with systemic symptoms	IIAF-SS	Drug-induced form of acne fulminans with systemic symptoms (rarely testosterone and anabolic steroids can induce this reaction; this entity is much less common than IIAF-WOSS)
Isotretinoin-induced acne fulminans without systemic symptoms	IIAF-WOSS	Drug-induced form of acne fulminans without systemic symptoms (other drugs including testosterone and anabolic steroids can induce IIAF-WOSS; this entity is the most common form of AF)

AF, Acne fulminans; *AF-SS*, acne fulminans with systemic symptoms; *AF-WOSS*, acne fulminans without systemic symptoms; *IIIAF-SS*, isotretinoin-induced AF with systemic symptoms; *IIAF-WOSS*, isotretinoin-induced acne fulminans without systemic symptoms.

as monotherapy for at least 4 weeks for AF-SS, and for at least 2 weeks for AF-WOSS. Corticosteroids should be continued until the crusted lesions have healed; then low dose isotretinoin (0.1 mg/kg/day) can be added. Subsequently, the corticosteroid therapy should continue and overlap with low dose isotretinoin for at least 4 weeks. Isotretinoin can then be gradually increased, with a slow taper of the corticosteroid. A recommended corticosteroid tapering regimen involves halving the dose each week to a physiologic dose, then every other day for 2 weeks. This taper will generally require a 4- to 8-week period of time. Thus, patients are commonly on systemic corticosteroids for a period of 3-4 months, and this treatment may be prolonged if the patient flares when the dose of isotretinoin is increased.

Given that the course of systemic corticosteroids may be prolonged, it is necessary to obtain a good baseline history and physical examination, ruling out concerns regarding risk for tuberculosis, presence of hypertension, diabetes, peptic ulcer disease, or psychiatric disorders. Most panelists do not use ulcer prophylaxis in low-risk patients, but this possibility may be discussed with patients.

If acne flaring occurs during the course of this treatment plan, then more prolonged systemic

Therefore, his diagnosis was consistent with acne fulminans with systemic symptoms (AF-SS). He was treated with prednisone 1 mg/kg monotherapy for 4 weeks, and then isotretinoin 0.1 mg/kg was added to his regimen for the subsequent 4 weeks. The patient showed dramatic improvement, allowing prednisone to be tapered with slow, incremental increases in his isotretinoin dosage. **C-E**, 12-year-old boy with inflammatory papules, pustules, and hemorrhagic crusts on the face (**C**), chest, and back (**D**). The lesions developed 4 weeks after initiating isotretinoin 30 mg/day with no systemic symptoms present. This patient was diagnosed with isotretinoin-induced acne fulminans without systemic symptoms (IIAF-WOSS), and isotretinoin was promptly discontinued. He received 2 weeks of prednisone 1 mg/kg monotherapy, at which time the hemorrhagic crusts and erosions had resolved (**E**). Isotretinoin 0.1 mg/kg was started and continued along with the prednisone 1 mg/kg for the subsequent 4 weeks. The patient was slowly tapered off of prednisone as he continued isotretinoin 0.1 mg/kg dose for another 4 weeks and until he was able to tolerate slowly increasing the dose of isotretinoin. His full course of isotretinoin therapy lasted 26 months with a final cumulative dose of 130 mg/kg. **F**, 16-year-old boy with papules, pustules, and scarring on the face, which is consistent with severe inflammatory acne. To prevent IIAF, the patient was administered prednisone 0.5 mg/kg for 2 weeks before initiating isotretinoin. He was then started on low-dose isotretinoin and did not experience a dramatic flare of inflammatory acne with crusting, erosions, or systemic symptoms.

Table II. Initial diagnostic evaluation of acne fulminans

Physical examination	Complete physical examination including temperature
Laboratory studies	- Complete blood count with differential - Liver function tests - Erythrocyte sedimentation rate and C-reactive protein (in patients with systemic findings) - Urine or serum human chorionic gonadotropin (in women)
Imaging	Radiograph (only if patient has symptoms concerning for bone or joint involvement)

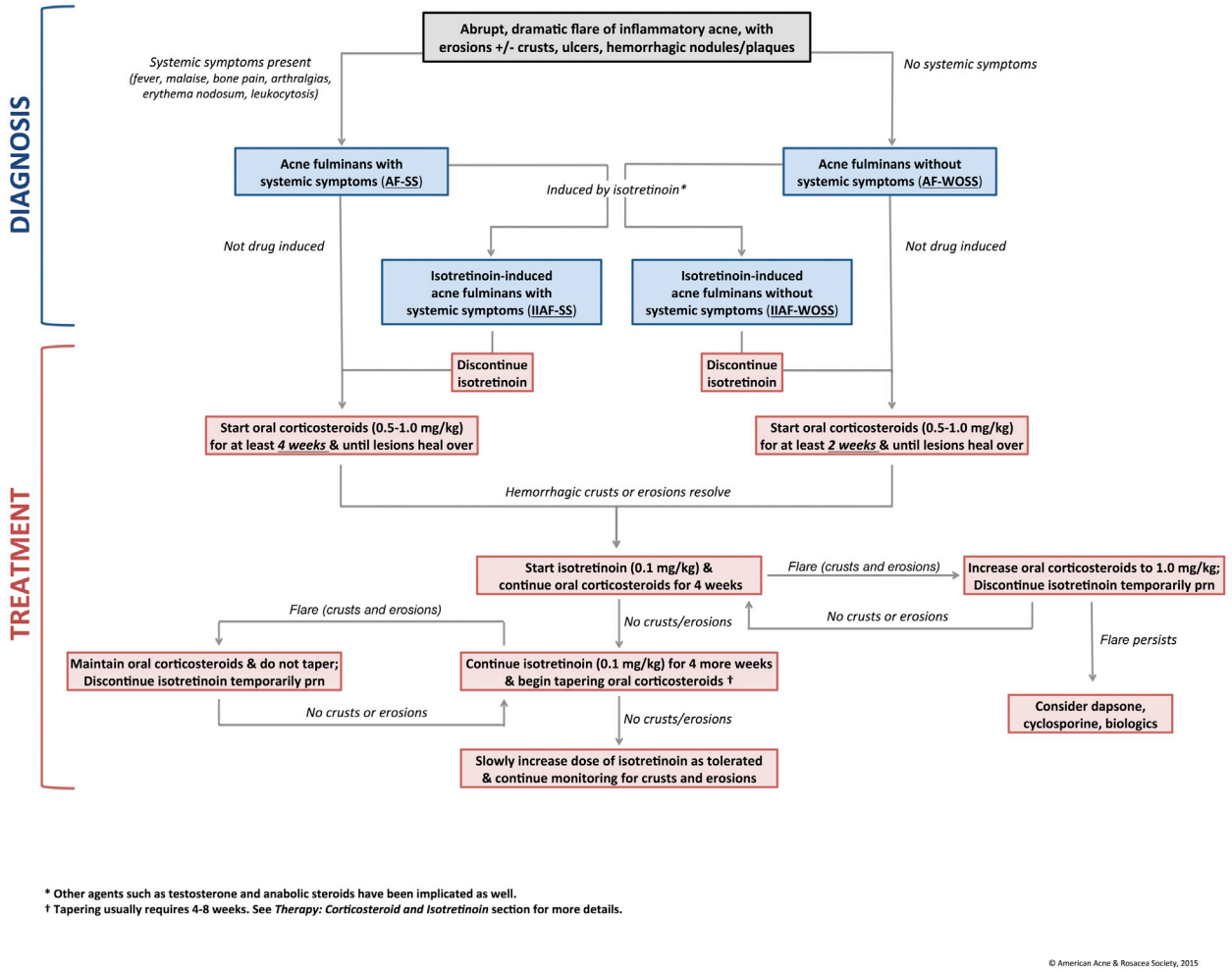

Fig 2. Consensus classification and treatment algorithm of acne fulminans and its variants. © American Acne & Rosacea Society. Printed with permission.

corticosteroid therapy or discontinuation of isotretinoin temporarily may be required (see algorithm, Fig 2).

The typical isotretinoin cumulative goal dose is 120-150 mg/kg.[1,11,26,27] Many patients with AF will require a longer course of treatment for their prolonged symptoms because the dose is initially quite low and should not be rapidly increased. In addition, refractory disease might require more prolonged therapy, which may be treated with higher cumulative doses of isotretinoin.

High-potency topical corticosteroids once to twice daily may be used for eroded sites associated with granulation tissue or even at sites of incipient erosion.[28] Such use could theoretically decrease the duration of systemic corticosteroid treatment. In patients unwilling or unable to tolerate oral corticosteroids, the use of high-potency topical corticosteroids in high-risk areas might be a reasonable option.

To prevent IIAF in a severe inflammatory acne patient (Fig 1, *F*), overlapping prednisone

(0.5 mg/kg/day to 1 mg/kg/day) for 2-4 weeks with concurrent low-dose isotretinoin should be considered. Isotretinoin should then be increased gradually over 3-5 months as tolerated. Some panelists institute prednisone as monotherapy for 2 weeks before starting isotretinoin, if concern is extremely high for induction of AF.

Antibiotics

Tetracyclines are not recommended as first-line treatment for AF. Most experts believe it is, at best, minimally effective.[1] Case series of AF showed poor clinical response to antibiotics alone.[1,4] The literature is unclear if there is an additional positive clinical response when used in combination with systemic corticosteroids as compared with systemic corticosteroids alone or corticosteroids with isotretinoin.[1,4] If used, in cases in which the patient is intolerant to isotretinoin or oral corticosteroids, maximum tetracycline dosing should be prescribed (doxycycline 100 mg twice daily, minocycline 100 mg twice daily, tetracycline 500 mg to 1 g twice daily).[4]

Prospective studies are required to determine if the use of oral antibiotics before or overlapping with the initiation of isotretinoin minimizes IIAF. Many panelists use systemic antibiotics to pretreat patients before instituting isotretinoin therapy in the belief that this decreases the risk of inducing IIAF; however, no evidence-based data exists to support this belief. Possible adverse effects following the concurrent use of isotretinoin and tetracylines include increased risk for pseudotumor cerebri syndrome (discussed below). Some panelists felt that the risk-benefit ratio for this approach is superior to the combination of systemic corticosteroids and isotretinoin; 38% of panelists use regimens of oral antibiotics overlapping with isotretinoin, while 62% do not. This is a controversial topic: 46% of panelists believe that the risk-benefit ratio argues against combination antibiotic-isotretinoin use, while 54% feel the risk is minimal.

Biologics

The biologic agents etanercept and infliximab have been successfully used to treat isotretinoin-resistant acne conglobata in a few case reports.[29-31] In addition, the acne lesions of SAPHO might respond to tumor necrosis factor−α inhibitors, primarily infliximab.[32-35] Tumor necrosis factor−α inhibitors, anakinra (an IL-1 receptor antagonist), and canakinumab (an anti−IL-1β monoclonal antibody) have reported efficacy in treating acne in PAPA and PAPASH syndromes.[36-39] No specific data regarding the use of biologics is available for AF. However, in recalcitrant cases, or in patients intolerant to isotretinoin, the panel agrees that the use of biologic agents should be considered.

Alternative and adjunctive therapies

Several novel approaches to managing AF have been reported. Alternative immunosuppressive and anti-inflammatory agents, such as cyclosporine and dapsone, have been successfully used in a small number of cases.[40-43]

Two patients with AF who were treated with the immunomodulator levamisole experienced immediate and sustained benefits.[44] The proposed mechanisms of levamisole include enhanced modulation of T-cell responses, macrophage functions, and increased neutrophil proliferation.[45]

Pulsed-dye laser applies a wavelength of 585-595 nm that targets hemoglobin and is proven effective in improving wound healing and acne scarring.[46] One case report used pulsed-dye laser to treat hemorrhagic erosions and excess granulation tissue in IIAF with improvement after 2 treatments.[46]

SPECIAL CONSIDERATION REGARDING SEVERE ADVERSE TREATMENT EFFECTS: PSEUDOTUMOR CEREBRI SYNDROME

Tetracycline, isotretinoin, and corticosteroids have been associated with the development of pseudotumor cerebri syndrome (PTCS). PTCS encompasses primary and secondary disorders of elevated intracranial pressure (ICP) caused by increased resistance in cerebrospinal fluid outflow.[47-49] PTCS usually causes headache and blurry vision and can result in permanent vision loss if unrecognized. The signs most suggestive of PTCS are postural headache, tinnitus, transient visual disturbance, and diplopia. Because no reliable feature of PTCS can distinguish it from migraine or tension headaches, dermatologists should have a low threshold for referring patients on isotretinoin, tetracyclines, or corticosteroids for dilated-eye examination to rule out papilledema. ICP remains elevated for weeks after discontinuing the responsible agent(s), and papilledema can persist for even longer; therefore, close neuro-ophthalmic monitoring and treatment with ICP-lowering medications such as acetazolamide are necessary.[50]

Primary PTCS predominantly occurs in obese adult females of childbearing age, whereas secondary PTCS has a specific cause, including systemic retinoid and tetracycline medications.[51-53] Proof of causation has been established for these classes by observing PTCS recurrence following medication rechallenge. Among tetracyclines, minocycline carries the highest risk for secondary

PTCS.[54] Synergistic risk of combination therapy with isotretinoin and a tetracycline has been suggested by case reports.[55] However, there are also reports of patients tolerating one class after developing PTCS from the other.[56,57] Importantly, corticosteroids have no clear association with PTCS, except in cases of abrupt withdrawal of chronic systemic corticosteroids.[58-66] The consensus of the panel was that concomitant use of tetracyclines with isotretinoin is not recommended as standard practice. However, if the provider and patient deem the potential benefit to outweigh the risk, overlapping use of doxycycline or tetracycline, but not minocycline, with isotretinoin could be considered, acknowledging the potential risk for PTCS.

FUTURE DIRECTIONS

The consensus panel acknowledges that there is a paucity of strong evidence addressing the pathogenesis and treatment of AF and its variants. AF with and without systemic symptoms is rare, but several case series exist that provide some guidance regarding management. Unfortunately, isotretinoin-induced disease is more common and appears to be increasing, but evidence-based data is similarly lacking for this disorder. Using a uniform classification system should simplify and optimize future investigations. Future areas of research include identifying at-risk groups, defining prevention strategies, and comparing drug dosing effects, as well as the impact of combination therapies. Better understanding of the mechanism of action of isotretinoin might also provide insight into the pathogenesis of AF. Genetic information, particularly immunogenetic profiling of patients, might provide insight into the spectrum of this disease, leading to more optimal directed therapies.

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