TNF-α inhibitors (etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol) have been used for more than a decade to successfully control the aforementioned conditions and others off label. Adalimumab is a fully human monoclonal antibody which specifically binds to membrane and soluble TNF-α with high affinity. Etanercept binds only soluble TNF-α and interestingly has more reports of treatment failure than success. This binding difference explains why TNF-α inhibitors cannot be used interchangeably.

Neutralizing anti-adalimumab antibody formation exists in 6-50% of psoriasis patients and is correlated with loss of efficacy, clinically more severe disease and higher measured serum TNF-α levels.14 – 17 A serum level appears to exist as higher anti-drug antibody titers predict loss of response and treatment failure.14 The titer level seems particularly important, as patients with low titers still had the same beneficial response as patients with no drug neutralizing antibodies.14 Higher sustained TNF inhibitor dosages and concomitant use of immunosuppressives like methotrexate were associated with lower anti-drug antibody formation.14 Therefore, it has been hypothesized that vacations from TNF inhibitor therapy and longer time on therapy raise the likelihood of antibody formation.10,12 In our patient, the 7 month drug holiday did not decrease clinical response.

Discussion

There have been numerous treatments for generalized granuloma annulare all with varying limited success. This case supports the recent article of 7 patients who had similarly impressive clearance with adalimumab in GA. Our case further illustrates successful re-challenging of adalimumab after disease recurrence.

Granuloma annulare can exist in many forms but is most commonly a self-limited, benign cutaneous disease that classically presents as annular plaques located on the extremities of young people. While benign, these lesions can cause significant cosmetic distress to the patient and cause social withdrawal. The cause of GA is unknown but insect bite reactions, sun exposure, trauma, tuberculin skin testing, IVH therapy, and viral infections have all been proposed as the initiating factor.6

Localized GA is the most common form followed by generalized but other subtypes exist including subcutaneous, perforating, and patch. Localized GA typically presents as well defined annular papules or plaques on arms, legs, hands, or feet.10

50% of patients will have more than one plaque and the face is almost never involved.6 Generalized GA is more widespread with papules and plaques coalescing together to involve large areas commonly on the trunk and extremities. Cosmeticly this can cause significant distress and social withdrawal. These areas usually spontaneously clear but can take up to a decade for complete resolution.6

Differential diagnosis for GA can be broad and vary widely depending on the specific morphologic of the lesion and its anatomical location. It is commonly mistaken for tinea corporis, but can be differentiated by the absence of scale. Anthropic biopsies can be a confounding diagnosis especially in the early papular stage. Other differential diagnoses include annular lichen planus, cutaneous sarcoidosis, tuberculosis leprosy or erythema annulare centrifugum.8

Tumor necrosis factor (TNF) is released by a variety of cells including macrophages and T lymphocytes in response to a variety of stimuli. TNF has numerous biologic effects including antiviral and antitumor activity. Tumor necrosis factor-alpha (TNF-α) is the prototypical member of a family of cytokines which are involved in proinflammatory responses, pro-apoptosis, cell activation, and granuloma formation in both infectious and noninfectious states.12 The concentration of TNF-α is elevated in several rheumatic diseases, such as psoriatic arthropathy, anklyosing spondylitis, rheumatoid arthritis, Crohn’s disease.12

Clinical Photographs

- Figures 1 and 2: Clinical photographs taken on initial presentation

Case Report

A 45 year old female presented to the office with a 9 month history of progressively enlarging rash on her lower legs (Figure 1 and 2). Patient denied any associated symptoms or precipitating factors, including fevers, chills, pruritus, joint aches, or recent infections. Past medical history was limited to seasonal allergies which she took loratadine daily.

Cutaneous examination revealed a Fitzpatrick type 3 patient with scattered erythematous plaques and papules on her bilateral lower legs. There was no overlying scale or ulceration, papulonodular, and indurated beta NGC. Due to the limited response of the prior medications, the use of adalimumab was discussed, along with a lengthy discussion regarding the risk and benefits, and the patient was agreeable to trial the medications.

Prior to starting therapy with adalimumab screening for hepatitis B, hepatitis C, and tuberculosis were performed, all of which were negative. The patient was started on an initial subcutaneous dose of adalimumab 80mg followed by 40mg doses every 2 weeks. Within 4 weeks of starting therapy, there was significant improvement of existing plaques with no new plaques noted. At 12 weeks there was limited post inflammatory hyperpigmentation, which was resolved completely at the 9 month visit. At this point, the adalimumab dosing began to be tapered slowly over an 8 month period.

Our patient remained clear for 7 months off adalimumab when she presented to the office with small pink annular plaques on both lower legs. Screening blood work was repeated and the patient was started on loading dose of adalimumab once again. Response was near identical to the first dosing with fading of plaques and no new areas at 3 month follow up. At the time of this case report being written, the patient remains clear and is in the tapering phase receiving adalimumab 40mg every 3 weeks.

Conclusion

Treatment of GA with adalimumab has been reported as successful in the literature,3,14,19 the importance of this case study is showing its tremendous efficacy when treating the patient after complete cessation of the medication. Further studies are needed to elucidate effective treatment protocols including dosing and length of taper. If further studies continue to show similar dramatic resolution of GA, we suspect that adalimumab will rapidly rise towards first line therapy of generalized GA. Practical utility of this treatment will be large barriers towards faster adoption.

Although a benign condition, it can have devastating psychosocial and cosmetic effects on patients and for this reason treatment options need further exploration.

Bibliography

11. Smart Guides will help you align it drag it into place. PowerPoint's multimedia file. Th