

Mini Review

Tetracyclines and Niacinamide as Steroid Sparing Agents in the Treatment of Autoimmune Bullous Diseases: A Short Review

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- Niacinamide
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Abstract

Niacinamide (nicotinamide), a physiologically active form of niacin (nicotinic acid), has a variety of potential mechanisms of action in the treatment of inflammatory skin diseases including its effects on leukocyte chemotaxis, lysosomal release, lymphocytic transformation, mast cell degranulation and decreased proinflammatory cytokine production. The tetracycline family of bacteriostatic antibiotics also has many anti-inflammatory mechanisms of action and has been used alone or in combination with niacinamide for a variety of inflammatory diseases. The goal of this short review is to summarize the data reported for these agents in the therapy of autoimmune bullous diseases. A comprehensive literature review showed efficacy as steroid sparing adjuvants in pemphigoid, pemphigus, linear IgA diseases and dermatitis herpetiformis. Few prospective trials exist but in aggregate these agents alone or in combination have reports of good responses in a total of 197/242 bullous pemphigoid patients, 34/43 cicatricial pemphigoid patients, 95/109 pemphigus patients, 7 linear IgA bullous dermatitis patients and 4 dermatitis herpetiformis patients. This is encouraging for future prospective trials to evaluate these agents and helps better define the role of tetracycline and niacinamide in steroid sparing medications for this challenging group of diseases.

ABBREVIATIONS

AIBD: Autoimmune bullous disease; LABD: Linear IgA bullous dermatosis; DH: Dermatitis herpetiformis; BP: Bullous pemphigoid; CP: Cicatricial pemphigoid; MMP: Mucous membrane pemphigoid; OCP: Ocular cicatricial pemphigoid; PG: Pemphigoid gestationis; HG: Herpes gestationis; PV: Pemphigus vulgaris; PF: Pemphigus foliaceus; TCN: Tetracycline, minocycline, doxycycline; NAM: Niacinamide or nicotinamide; Combination therapy with a tetracycline + niacinamide (TCN/NAM)

INTRODUCTION

Tetracyclines (tetracycline, minocycline and doxycycline) are bacteriostatic antibiotics with a variety of anti-inflammatory properties that have been used widely throughout dermatology [1]. These include: decreases in lymphocyte mitogenic responses, antibody production, complement activation, chemotaxis of neutrophils and eosinophils, prostaglandin synthesis, and inhibition of various tissue enzymes including collagenase, lipase and tissue metalloproteinases 2 and 9 [2,3].

Niacinamide (NAM, aka nicotinamide) is one of the dietary forms of NAD precursors which are important for their role in

NAD/NADPH pathway of electron transport (Canto et al 2012). NAM has an amide side chain that prevents the vasodilatory flushing and hypotension that can be associated with high doses of niacin (aka nicotinic acid) supplementation. NAM has been associated with a wide range of biochemical and immunologic effects when used in higher doses including free radical scavenger function, inhibition of phosphodiesterase and other proteases, stimulation of adenylyl cyclase, driving tryptophan metabolism to increase serotonin, inhibition of lymphocyte mitogenic responses, suppression of IgE-mediated release of histamine from mast cells and degranulation of neutrophils and eosinophils [4,5].

Recently it has been hypothesized that many autoimmune processes result in NAD depletion via combination of persistent indoleamine 2,3 dioxygenase (IDO) activation and iNOS-peroxynitrite activation of nuclear enzyme poly(ADP-ribose) polymerase 1 (PARP-1). PARP-1 plays a significant role in DNA repair, maintenance of genomic stability, and cellular response to injury including inflammation and apoptosis and NAM supplementation has been shown to be an inhibitor PARP-1 [6,7].

These pathways may explain why NAM supplementation has beneficial effects in a wide range of inflammatory diseases

including: rheumatoid arthritis, type 1 diabetes, multiple sclerosis, colitis, depression, hyperkinesia, epilepsy and schizophrenia in patients or in animal models. NAM also has reported uses as a radiosensitizer, inhibitor of tumor promoter genes, and slow metastatic spread of experimental cancers and prevents carbon tetrachloride induced hepatotoxicity in rats. Dermatologic uses including: autoimmune bullous diseases, necrobiosis lipoidica, granuloma annulare, polymorphous light eruption, acne, aphthous ulcers, erythema elevatum diutinum, atopic dermatitis, pellagra, Hartnup disease, and discoid lupus in dogs [4,9,10]. In acne lesions, there is also activation of transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and activator protein 1 (AP-1), which is inhibited by NAM through PARP-1 inhibition [5]. This brief review will summarize the published data using TCN and/or NAM as steroid sparing adjuvants in autoimmune bullous diseases.

METHODS

Pubmed.gov and Google Scholar searches were done in August 2020 with MESH terms of pemphigoid, pemphigus, linear IgA bullous dermatosis (LABD), chronic bullous disease of childhood, dermatitis herpetiformis (DH), bullous pemphigoid (BP), localized pemphigoid, cicatricial pemphigoid (CP), mucous membrane pemphigoid (MMP), ocular cicatricial pemphigoid (OCP), Brunstig-Perry pemphigoid, radiation induced pemphigoid, pemphigoid gestationis (PG), herpes gestationis (HG), pemphigus vulgaris (PV), pemphigus foliaceus (PF), pemphigus vegetans, treatment, therapy, tetracycline, minocycline, doxycycline, niacinamide and/or nicotinamide. All studies with retrievable abstracts or full text articles were reviewed and any that contained treatment outcomes for one or more patients with any of the tetracyclines (collectively abbreviated TCN throughout the results and discussion), niacinamide or nicotinamide (abbreviated NAM throughout the results and discussion) or a combination of any tetracycline plus niacinamide (abbreviated TCN/NAM throughout the results and discussion) were included in the results.

RESULTS

Large and small cases series or single case reports were all included, but distinction between partial responders from complete responders and those that were monotherapy vs adjuvant therapy to aid in steroid sparing was not possible, thus all results are reported for any responders vs nonresponders to allow aggregation of data. The results are presented by disease entities and the reference list is organized to match each group of diseases.

Bullous Pemphigoid

Berk and Lorincz first reported 4 patients to respond to tetracycline and NAM in 1986. The author received a FDA-Orphan Products grant in 1990 for the only double blind trial of these agents in comparison to steroid monotherapy published to date, enrolling 20 patients over 3 years with 12 TCN/NAM responders and 8 steroid responders [11]. Including these reports, there have been a total of 180/225 patients reported with BP responding to TCN/NAM [11-17]. There have also been 12/12 patients reported treated with TCN monotherapy [18-21].

Localized BP has only been reported twice. A single case in a breast reconstruction site was treated successfully with just NAM [22] and another with just TCN [23]. **Radiation induced BP** was treated successfully in 3/3 patients with TCN/NAM and 1 with just TCN [24-27].

Cicatricial Pemphigoid case reports and small series favored TCN monotherapy as adjuvants to steroids or other immunosuppressors with 25/30 reported responders [28-32]. TCN/NAM was reported as effective in 9/12 cases [29,33-36].

Lichen Planus Pemphigoides and P200 Pemphigoid are both very rare forms of subepidermal bullous disease and each has had a single case report of TCN/NAM therapy being effective, [37,38].

Pemphigoid Gestationis (Herpes Gestationis) has been reported in 2 publications and a total of 3 patients. All 3 were treated with doxycycline and niacinamide with no adverse pregnancy outcomes reported [39,40].

Dermatitis Herpetiformis

DH has been reported to be effectively treated with TCN/NAM in 4 patients in 3 publications [41-43].

Linear IgA Bullous Disease

LABD has been reported to be effectively treated with TCN/NAM by us and others totaling 6 patients and dapsone was combined with NAM in one patient [44-49].

Pemphigus vulgaris

PV has several cases series as well as numerous case reports of TCN/NAM therapy. One of the largest has been from the author's patient population that was analyzed and reported in 2014 and updated with more strict outcome parameters in a publication this year with a total of 60/67 patients being responders [50,51]. In aggregate, there have been 66/74 TCN/NAM patients reported as responders with pemphigus and 20/24 with TCN monotherapy. Almost all series were patients initially treated with oral steroids with the TCN/NAM therapy used as a steroid sparing adjuvant [45,50-54].

Pemphigus foliaceus has been reported as effectively responding to TCN/NAM in 7 of 8 patients in 4 different publications including 4 of 5 from our patient population [45,56-58].

Rare forms of pemphigus including **pemphigus vegetans** (n=2) and **pemphigus herpetiformis** (n=1) have been reported to be effectively treated with TCN/NAM [59,60].

DISCUSSION

In the late 1940's to early 1950's there were numerous case reports of pemphigus treatment with chlortetracycline (aka Aureomycin- the first form of TCN produced in first in 1945) alone or in combination with the antimalarial agent quinacrine. However this agent is no longer in use and it was not until 1984 that TCN/NAM was reported [12]. The use of TCN and/or NAM separately or in combination appears to be effective steroid sparing agents in the AIBDs based on the findings summarized here.

AIBDs as a group are challenging to treat due to their necessity of relatively aggressive immunosuppression being needed to gain disease control in many presentations.

Steroid sparing agents traditionally used in AIBDs include dapsons, IVIG, methotrexate, mycophenolate mofetil, azathioprine, as well as newer targeted immunobiologics like rituximab [61]. Side effects related to most of these steroid sparing agents can be dose limiting and result in considerable increased morbidity and mortality. While side effects of TCN (photosensitivity, GI upset, etc.) and NAM (very rare flushing, GI upset, abnormal liver enzyme levels) are reported, caution with minocycline use in this patient population is warranted as dyspigmentation, vertigo, pseudotumor cerebri and autoimmune pneumonitis or hepatitis have all been seen with its use [62,63].

As mentioned in the introduction, TCN/NAM has also been used in a variety of other dermatologic conditions and is well known for its utility in veterinary dermatology as well [64]. The long track record of this combination and diverse applications make it a good option as first line steroid sparing therapy.

LIMITATIONS

Many reports are single case reports and most of the series reviewed were retrospective and tetracycline(s) or NAM was often used as adjuvant therapy during steroid reduction. Partial responses vs complete responses were not clearly delineated in most articles so all responders were included in this review.

CONCLUSIONS

The combination of TCN/NAM has a growing literature for its utility as a steroid sparing regimen in the autoimmune bullous diseases. BP and PV have the most robust support in the literature. Prospective and randomized double blind studies are needed to properly assess the impact of these agents singularly or in combination.

However, given that these are older agents with long track records of use and both are available as generic or over the counter products, it is reasonable to consider their use in the management of blistering diseases.

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