International Journal of Women's Dermatology 2 (2016) 77–84

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

A dermatologist guide to immunogenicity☆,☆☆

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ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form 26 April 2016
Accepted 5 May 2016

Key words:
antidrug antibodies
autoantibodies
biologic fatigue
HACA antibodies
resistance to biologics

ABSTRACT

Dermatologists should be aware that autoantibody formation may occur after the initiation of biologic therapy. This phenomenon has been referred to as immunogenicity and biologic fatigue. Because of this, patients may experience loss of clinical efficacy to a particular drug. To combat this phenomenon, low-dose immunomodulators may be used in hopes of preventing autoantibodies. We review the current literature and provide a basic treatment algorithm for patients with moderate to severe psoriasis.

Introduction

Biologic agents were marketed to dermatologists as single drug therapy, but when marketed to gastroenterologists and rheumatologists, they were recommended as a supplement to other medications. Manufacturers eventually recognized that immunomodulators like methotrexate (MTX), azathioprine (AZA), and mercaptopurine (6-MP) reduced the production of autoantibodies against tumor necrosis factor alpha (TNFα) agents (Remicade, 2013). These data suggested that supplemental therapy with immunomodulators might prolong the efficacy of biologics when compared to TNFα monotherapy.

Biologics (with the exception of infliximab) are fully human monoclonal antibodies, so the immune response theoretically should be quiescent (Scott and De Groot, 2010). However, the immune system can unexpectedly produce anti-drug antibodies (ADA), resulting in decreasing efficacy of the biologics (Scott and De Groot, 2010). This effect was found among many biologics (the anti-TNFα agents adalimumab, infliximab and etanercept, and the anti-p40 [interleukin 12/23] ustekinumab), and many patients have been placed on an alternate biologic treatment regimen. The loss of efficacy has been partially attributed to neutralizing ADA formation against the biologic drug. These ADA lead to the formation of drug-antibody complexes that accelerate drug clearance from the circulation and subsequently inhibit function (Carrascosa et al., 2014).

Several factors may contribute to immunogenicity, including some that are extrinsic to the molecule (Scott and De Groot, 2010). Intravenous administration favors immunogenic tolerance, while subcutaneous or intramuscular injection favors a secondary immune response to inflammation from the injection site and drainage to local lymph nodes (Scott and De Groot, 2010). Antigen presenting cells (dendritic cells) are abundant in the skin, but the patient's human leukocyte antigen type governs whether T-cell epitopes derived from the biologic are presented to T cells (Scott and De Groot, 2010). Patients with psoriasis (PsO) may have an inherent T-cell defect that increases immunity to a given drug; that is, the disease promotes immunogenic responses to proteins that might not normally trigger one (Scott and De Groot, 2010). A brief discussion regarding the use of combining biologics and MTX for the treatment of Crohn's disease and rheumatoid arthritis (RA) are also provided.

Methods

A systematic English-language literature search was conducted of both PubMed and MEDLINE databases from inception through December 10, 2014, to identify trials of biologics and MTX for the treatment of PsO and psoriatic arthritis (PsA). Key search terms

☆ Funding source: none.
☆☆ Conflicts of interest: none.
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http://dx.doi.org/10.1016/j.ijwd.2016.05.001

Table 1
Selected publications on combination therapy of biologics with MTX in PsO

Reference	Study type	Number of patients with biologic and MTX/mean duratiof tx weeks	Biologic and average MTX dose/other systemic agent	Timing of MTX	Efficacy	Antibody Levels	Tolerability
Lopez-Ferrer et al. BrJ Dermatol 2013; 169; 1141-7	Retrospective	26/24	Adalimumab 40mg eow 5 ± 12.5mg MTX/week[2]	Add-on MTX when insufficient response to Adalimumab	After 24 weeks Combination group 73.5% PASI 75 67.5% PASI 90 Monotherapy group 43.5% PASI 75; 34.8% PASI 90	Did not measure	Infections, including de novo infection by Mycobacterium tuberculosis, accounted for most SAEs, and paradoxical flares of psoriasis and psoriatic arthritis were relatively frequent in daily clinical practice.
Philipp et al. J Dtsch Dermatol Ges 2012 10: 821-37	Retrospective	32/43	Adalimumab 40mg eow 12.4 ± 4.5mg MTX/week	20 patients received MTX concomitantly 12 patients received add on MTX when insufficient response to Adalimumab	85% PASI 50-75[1] 67% PASI 50-75[1]	Prevention of anti-ADA antibodies was the reason in 3/32 patients for combination therapy with ADA and MTX.	Eighteen patients experienced 24 adverse events; none was severe and/or required hospitalization. More data are needed to determine the long-term safety and efficacy of these combinations
Van den Reek et al. J Dermatolog Treat 2013; 24: 361-8	Prospective	11/24	Adalimumab 40mg eow 9.5 ± 3.2mg MTX/week	Add-on MTX when insufficient response to adalimumab	After 12 weeks 9% PASI 50 After 24 weeks 18% PASI 50	Twenty-five percent of first treatment episodes with adalimumab dose escalation induced a PASI50 response after 12 weeks and 35% after 24 weeks. Addition of MTX to adalimumab every other week resulted in PASI50 in 9% after 12 weeks and 18% after 24 weeks.	No related serious adverse events were reported.
Dalaker et al. J Eur Acad Dermatol Venereol 2009; 23: 277-82	Retrospective	18/106	Infliximab 3-5mg/kg 11.66 mg MTX/week[2]	MTX started concomitantly	After 14 weeks 91.3% PASI 50 69.6% PASI 75 39.1% PASI 90 After 1 year 80% PASI 50 60% PASI 75 33.3% PASI 90	6-year-old boy, received infliximab 5 mg/kg instead of 3 mg/kg in combination with methotrexate EXPRESS trial with 5 mg/kg infliximab monotherapy with detectable preinfusion serum infliximab concentrations: maintained maintained their PASI 75 response over time; \ undetectable serum infliximab concentrations (below 0.1 g/mL), less likely to maintain response. 5	Combination regimens of infliximab with methotrexate or azathioprine were well tolerated, and only one patient discontinued therapy because of an adverse event (lung embolism) after two infusions with infliximab.
Driessen et al. Br J Dermatol 2008; 159: 460-3	Prospective	14/40	Etanercept 50mg twice weekly the first 12 weeks, than 25mg twice tweekly 12.5mg[2] MTX/week	8 patients started with MTX and received add-on etanercept 6 patients recived add-on MTX when insufficient response to etanercept	Discontinuation of MTX in 6 of these patients resulted in a decrease in clinical efficacy in 5 patients[3] 67% improvement efficacy[3]	Did not measure	Etanercept combined with methotrexate was well tolerated, and only mild adverse events were reported.
Zachariae et al. Acta Derm Venereol 2008; 88: 495-501	Prospective	31/24	Etanercept 50mg twice weekly the first 12 weeks, than 25mg twice weekly 13.4mg[2] MTX/week	Add-on etanercept when insufficient response to MTX Etanercept with MTX tapered treatment	After 24 weeks combination group 76.4% PASI 75 Tapered MTX group 51.3% PASI 75	Did not measure	Very little difference between the two groups; The most common organ system class affected by adverse events was infections, where 7 (25.0%) and 12 (38.7%) adverse events were reported for the etanercept/methotrexate taper and combination groups, respectively.
Antoniou et al. J Eur	Retrospective	11/24	Etanercept 50mg twice	MTX started concomitantly	After 24 weeks	Did not measure	Etanercept was generally well tolerated.