REVIEW

Status Report on Topical Hypochlorous Acid: Clinical Relevance of Specific Formulations, Potential Modes of Action, and Study Outcomes

by JAMES Q. DEL ROSSO, DO and NEAL BHATIA, MD

Dr. Del Rosso is with JDR Dermatology Research/Thomas Dermatology in Las Vegas, Nevada and Touro University Nevada in Henderson, Nevada. Dr. Bhatia is with Therapeutics Clinical Research in San Diego, California.

J Clin Aesthet Dermatol. 2018;11(11):36–39

ABSTRACT

In-vitro and *in-vivo* studies have supported antimicrobial, anti-inflammatory, and other biologic properties of hypochlorous acid (HOCl), which has led to its use in the treatment of skin wounds, pruritus, diabetic ulcers, and some inflammatory skin disorders. Research has also shown that the physiochemical properties of HOCl after application to skin are highly dependent on both pH and formulation stability. In this review, the authors discuss a core HOCl formulation (Microcyn® Technology, Sonoma Pharmaceuticals, Petaluma, California) that is stable for up to two years, noncytotoxic, and pH-neutralized to augment therapeutic activity, skin tolerability, and stability. The authors summarize relevant study outcomes and potential modes of action related to this core HOCl formulation, as well as describe its ready-to-use vehicles that are approved and available for topical application.

KEYWORDS: hypochlorous acid, Microdacyn®

Hypochlorous acid (HOCl), a naturally occurring molecule that is a component of the human innate immune response, is recognized as a major active component of bleach and demonstrates antimicrobial properties supported by both *in-vitro* and *in-vivo* studies.[1–9] One important function of HOCl in host immunity is its release by neutrophils to destroy pathogenic organisms (i.e., respiratory burst). Over time, a variety of anti-inflammatory and other biologic properties of HOCl have led to applications for wound healing, pruritus, and diabetic ulcers, as well as applications for the management of some inflammatory skin disorders, such as seborrheic dermatitis and atopic dermatitis (AD).[8–18] What has also come to light is that the physiochemical properties of HOCl and its impact after application to skin are highly dependent on both pH and formulation stability.[8,11] The use of HOCl in the clinical setting is supported by a substantial body of research, which has led to the use of a core formulation—available in ready-to-use, approved topical vehicles—that is stable for up to two years, noncytotoxic, and, importantly, pH-neutralized to augment therapeutic activity, skin tolerability, and stability.[8,11,18,19] This core formulation (often referred to in the literature as a *superoxidized solution* or, sometimes, *slightly acidic electrolyzed water*) has been termed and marketed as Microcyn® Technology (Sonoma Pharmaceuticals, Petaluma, California; also referred to in some publications as Dermacyn™ from Dyamed Biotech Pte Ltd., Singapore).[8,11,20–22] In this article, we've summarized the available studies related to the core formulation, its available vehicles for topical application, its potential modes of action, and *in-vitro* and *in-vivo* study outcomes.

HOCl AS AN INTEGRAL COMPONENT OF TOPICAL FORMULATIONS USED IN THE MANAGEMENT OF VARIOUS SKIN DISORDERS

HOCl has been incorporated into topical formulations due to antimicrobial, anti-inflammatory, immunomodulatory, and wound healing properties.[1,6,8,10,11,17,20–22] The central microbicidal role of HOCl as a component of an innate immune response to combat pathogens within human phagocytic cells (i.e., neutrophils, monocytes, macrophages) is a pivotal concept in

FUNDING: No grants related to this project were provided. The authors receiverd honoraria as consultants to IntraDerm Pharmaceuticals for data review and manuscript accuracy.

DISCLOSURES: Drs. Del Rosso and Bhatia have received honoraria as advisors and research consultants for IntraDerm Pharmaceuticals.

CORRESPONDENCE: James Q. Del Rosso, DO; Email: jqdelrosso@yahoo.com

appreciating the potential therapeutic value of HOCl.[11] The antimicrobial activity of HOCl is not that of a conventional antibiotic but rather an agent that is directly toxic to microbial cells, including many gram-positive and gram-negative bacteria (e.g., *Staphylococcus aureus*, *Pseudomonas aeruginosa*) and their biofilms.[1–7] However, it is important to understand the relative balance of HOCl versus other reaction byproducts that are produced in equilibrium after the HOCl solution is applied. Formulation stability, pH, and resultant chemical reactivity influence the relative concentrations of HOCl, as compared with other byproducts (e.g., hypochlorite [-OCl]), which directly impacts the magnitude of antimicrobial activity, clinical effects, and potential irritancy of topical HOCl formulations.[11,20,21] In highly acidic pH (pH<3.5), HOCl markedly decreases with the production of multiple byproducts while, in a higher alkaline environment (pH>5.5), much of the HOCl is converted to -OCl.[11] HOCl stability is optimized over a pH range of 3.5 to 5.5.[11] Stabilized/pH-neutral HOCl is superior in terms of antimicrobial activity to nonstabilized HOCL and acidified bleach *in vitro*, including against hypochlorite-resistant strains.[5,11,21] This cumulative fundamental understanding of the physiochemical properties of HOCl led to the development of the stabilized and pH-neutral core formulation of HOCl solution mentioned previously (Microcyn® Technology) and its incorporation into different vehicles that allow for ease of application in clinical practice.[8,22] Existing studies evaluating the antimicrobial effects of HOCl are summarized in Table 1.

In addition to antimicrobial effects, other biologic properties of HOCl are likely to be clinically relevant. In a variety of laboratory studies, HOCl has been shown to decrease the activity of histamine, neutrophil-generated leukotrienes (i.e., LTB4), interleukin (IL)-6 and IL-2, and, in high concentrations, to downregulate some matrix metalloproteinases (MMPs) (e.g., MMP-7, collagenases), diminish mast-cell degranulation and cytokine release induced by immunoglobulin E, and induce favorable effects on keratinocyte and fibroblast migration.[1,10,11,17,22,23] The reduction of superantigen-producing *S. aureus* on atopic skin by HOCl application might also be a mechanism for a decrease in cutaneous inflammation associated with both eczematous dermatitis and pruritus in AD.[1,9,11] Both antimicrobial and anti-inflammatory/immunomodulatory properties appear to correlate with clinical benefits of HOCl when used for the treatment of various skin disorders, including AD/atopic skin, seborrheic dermatitis, lower extremity diabetic ulcers, pruritus, and acne vulgaris.[1,6,9,11–18] Other clinical applications include promotion of wound healing and scar prevention.[14–16,24]

COMPLETED STUDIES SUPPORTING ANTIMICROBIAL ACTIVITY AND OTHER POTENTIAL CLINICAL APPLICATIONS OF HOCL

There are several publications that include discussion and review of the antimicrobial properties of HOCl and topically applied stablilized/pH-neutral HOCl; methodologies have included preservative time-kill testing, microbial reduction studies on forearm skin with rechallenge, microbial analyses of diabetic foot ulcers, microbial analyses of atopic skin, and skin preparation studies.[1–9,14–16] Other publications discuss specific clinical applications using a variety of parameters to determine study outcomes. Table 1 depicts details from major studies that address the antimicrobial effects and other therapeutic properties and applications with use of stablilized/pH-neutral HOCl.

SUMMARY

HOCl exhibits broad-spectrum antimicrobial activity that is directly toxic to many bacteria and fungi and might also impart antiviral properties. Hypochlorous acid exhibits anti-inflammatory and immunomodulatory properties based on multiple laboratory analyses. These properties appear to correlate with the potential therapeutic benefits of topically applied HOCl for a variety of skin disorders. Topical formulations of stabilized, pH-neutral HOCl (e.g., solution, gel, spray) have been evaluated in several studies demonstrating both antimicrobial effects and therapeutic benefit in many cutaneous disorders, including seborrheic dermatitis, atopic dermatitis-associated pruritus, acne vulgaris, diabetic foot ulcers, and hypertrophic scars/keloids. Topical HOCl appears to be well tolerated and safe, without any major adverse events reported.

REFERENCES

1. Sakayra S, Gunay N, Karakulak M, et al. Hypochlorous acid: an ideal wound care agent with powerful microbicidal, antibiofilm, and wound healing properties. *Wounds.* 2014;26(12):342–350.
2. Day A, Abdulnaster A, Carney B, et al. Disruption of biofilms and neutralization of bacteria using hypochlorous acid solution: an in vivo and in vitro evaluation. *Advances Skin Wound Care.* 2017;30(12):543–551.
3. Issa-Zacharia A, Kamitani Y, Tiisekwa A, et al. In vitro inactivation of *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella* spp using slightly acid electrolyzed water. *J Biosci Bioeng.* 2010; 110(3):308–313.
4. Sauer K, Thatcher E, Northey R, et al. Neutral super-oxidized solutions are effective in killing *P. aeruginosa* biofilms. *Biofouling.* 2009;(25(1): 45–54.
5. Dardine J, Diaz L, Matinez C, et al. Activity of a pH neutral superoxidized solution against bacteria selected for sodium hypochlorite resistance. Poster L-1144 presented at the 47th ICAAC Meeting. Chicago, IL; 17–20 Sep 2007.
6. Fowler J. Antibacterial activity of Microcyn gel formulation containing hypochlorous acid. Poster presented at Winter Clinical Dermatology Conference 2016; Koloa, Hawaii; 15–20 Jan 2016.
7. Taketa-Graham M, Gutierrez AA, Thatcher E. The anti-viral efficacy of a new super-oxidized solution. Poster L-1144 presented at the 47th ICAAC Meeting. Chicago, IL; 17–20 Sep 2007.
8. IntraDerm Pharmaceuticals. Data on file.
9. Sasai-Takedatsu M, Kojima T, Yamamoto A, et al. Reduction of *Staphylococcus aureus* in atopic skin lesions with acid electrolytic water—a new therapeutic strategy for atopic dermatitis. *Allergy.* 1997;52(10):1012–1016.
10. Medina-Tamayo J, Sanchez-Miranda E, Ballez-Tapia H, et al. Super-oxidized solution inhibits IgE-antigen induced degranulation and cytokine release in mast cells. *Int Immunopharmacol.* 2007;7(8):1013–1024.
11. Pelgrift RY, Friedman AJ. Topical hypochlorous acid as a potential treatment for pruritus. *Curr Derm Rep.* 2013;2(3):181–190.
12. Draelos Z. An evaluation of oculus sebuderm-Microcyn based gel on mild to moderate facial and scalp seborrheic dermatitis. Poster presented at the 10th Annual Coastal Dermatology Symposium; Sonoma, CA: 24–27 Sep 2014.
13. Berman B, Nestor M. Investigator-blinded, randomized study evaluation of HOCl in the treatment of atopic dermatitis-associated pruritus. Poster presented at the Fall Clinical

TABLE 1. Existing studies evaluating mechanisms of action of HOCl

MECHANSISM OF ACTION	STUDY	METHODS	STUDY OUTCOMES/CLINICAL USE
ANTIMICROBIAL EFFECTS	Reduction of *S. aureus* in AD skin lesions;[9] HOCl solution evaluated using spray application	HOCl vs. water BID for 1 week; N=20 pediatric subjects; evaluations at 3mins and 7 days	Marked reduction in *S. aureus* colony counts in HOCl group; no change with water; superior clinical improvement in HOCl group in AD grading ($P<0.01$)
	In-vivo evaluation of bacterial reductions of *S. aureus* on healthy forearm skin (n=6); *in vitro* time-kill study vs. different bacterial and fungal isolates;[6] HOCl gel formulation evaluated	Colony counts/log reductions in growth assessed postincubation; rechallenge on 3 other subjects at later date; total of 60 sites tested *in vivo*; *in-vitro* time-kill testing completed on 23 bacterial and fungal isolates at timepoints up to 5mins	99.9% bacterial reduction was shown in *in-vitro* study inclusive of multiple bacteria (e.g., *S. aureus* [MRSA], *S. pyogenes*, *Klebsiella* spp, *P. aeruginosa*, *Enterobacter* spp, *Proteus mirablis*, *C. difficile* spores, others) and *Candida albicans*
	Inactivation of *S. aureus*, *E. coli*, and *Salmonella* spp *in vitro*;[3] HOCl solution evaluated	HOCl vs. sodium hypochlorite vs. water in chamber suspensions with fixed bacteria colony counts	Bactericidal effect markedly greater with HOCl vs. comparators ($P<0.05$); bacteria reduction did not correlate with available chloride concentration
	Evaluation of different HOCl solutions in inactivating viability of *P. aeruginosa* biofilms; included quantitative and ultrastructural evaluation[4]	Three formulations of neutral-pH HOCl solution tested (varying free chlorine concentrations)	Established HOCl fomulations that effectively caused biofilm disaggregation and >3-log reduction within 30mins
	Evaluation of stabilized/pH-netrual HOCl solution vs. bacteria resistant to domestic bleach/sodium hypochlorite;[5] comparisons completed vs. nonstabilized HOCl solution and domestic bleach	Cell suspensions of fixed colony counts of 10 resistant isolates tested after timed exposures to test products; bacterial reduction compared at multiple timepoints; primary comparison at 2mins	Bacterial reductions with stablized/pH-neutral HOCl greater and more consistent than comparators; stabilization/pH neutrality shown to increase antimicrobial activity of HOCl; activity of HOCl confirmed vs. resistant bacterial strains
	Bacterial susceptibility, time-kill testing (*S. aureus*, *P. aeruginosa*, *C. albicans*);[1] HOCl solution evaluated	MBC testing; time-kill study evaluating time of complete growth absence; biofilm eradication assessed in growth wells	Rapid time-kill of organisms with MBC range of $^{1}/_{32}$–$^{1}/_{64}$; biofilm magnitude and organism content within biofilms were decreased; dose-dependent response in a species-specific manner
	Antiviral activity *in vitro* including enveloped and nonenveloped virus types;[7] assessed poliovirus-1, rhinovirus-1, respiratory syncytial virus, HSV-1, HSV-2, influenza A H1 and H3, West Nile virus, and Norwalk virus surrogate; HOCl solution evaluated	Target cells infected with HOCl-treated or saline-treated (control) virus exposed for 1min and 5mins; cells in 48-well culture plates infected with either treated virus, incubated, and evaluated for cytopathic changes at 24–48hrs	Collectively, HOCl-exposed enveloped and nonenveloped viruses decreased by a $\log_{10}$ factor ≥5 with exposure of at least 1min; complete virus inactivation occurred within 5 mins
INFLAMMATORY SKIN DISORDERS/PRURITUS	HOCl gel in mild-to-moderate seborrheic dermatitis (n=25) affecting face and/or scalp;[12] open study; monotherapy; gel vehicle with dimethicone 2%	Application BID for 28 days; evaluations included IGA, SGA, pruritus, burning, and stinging	Endpoint success by IGA was 33% at Day 14 and 52% at Day 28; SGA of efficacy/improvement compared with baseline was 62% at Day 28; patients demonstrated improvements in pruritus and decrease in scaling
	HOCl gel evaluated for treatment of pruritus associated with AD (n=29)[13]	Investigator-blinded, randomized 72-hr study; included 19 treated with HOCl BID/PRN and 10 untreated (control); pruritus score of ≥2 on a 4-point scale (AD patients); evaluations included IGA, PGA, and VAS; IGA evaluation included erythema, lichenification, desquamation, and excoriation, and PGA included peeling, stinging, itching, and burning; VAS itch score was linear placement to assess severity (0mm=none, 154mm=most itching)	Mean changes from baseline noted in IGA and PGA were greater in the HOCl arm vs. untreated (control) (P=0.012 and P=0.128); mean % change in VAS itch score was improved significantly in HOCl group (-34.78) compared with untreated (control) group (+24.56) (P=0.007); 73.7% of HOCl group and 30.0% of untreated group noted a reduction in pruritus from baseline to 72hrs.
	HOCl solution evaluated for treatment of facial acne vulgaris (n=87);[18] HOCl solution (n=39) vs. BP (n=24) vs. placebo (n=24)	Double-blind, randomized, placebo-controlled, 12-week study; both actives and placebo applied BID to face; inclusion: 10–50 inflammatory papules/pustules (mean range: 33.5–35.3); no nodules; age range was 15–22 years; 46 women/41 men	Clinical improvements (excellent, good) comparable between HOCl and BP (23% vs. 21% and 54% vs. 50%, respectively); both HOCl and BP were markedly superior to placebo; there was no need for dosage adjustments in any groups and there were no local AEs.
DIABETIC FOOT ULCERS/ POSTSURGICAL WOUNDS/ SCARS	Open-label study of presurgical response to HOCl solution (n=110) vs. PI solution (n=108) in infected diabetic foot wounds/ulcers; evaluated as part of comprehensive wound care regimen[15]	Alternative assignment to be treated with HOCl or PI + daily dressing changes; baseline and postsurgical colony counts, healing time, and skin reactions noted; baseline number of bacteria similar in both groups	Significantly greater bacterial clearance in HOCl group ($P<0.001$); significantly shorter median healing time in HOCl group (43 days) vs. PI group (55 days) ($P<0.0001$); no adverse skin reactions in HOCl group (0/110) vs. 18 in PI group (18/108)
	Postsurgical therapy of infected diabetic foot ulcers healing by second intention (n=40);[14] HOCl solution evaluated vs. PI + systemic antibiotic therapy and surgical debridement; exclusions included renal failure and immunosuppression	Patients were followed up weekly over 6mos; evaluation of healing rate, time to negative cultures, duration of antibiotic therapy, number of reinterventions, and AEs were completed	Superior healing rates at 6mos in HOCl group (90% vs. 55%); $p<0.01$) were noted; significantly shorter time to negative culture and duration of antibiotic use in HOCl group ($P<0.05$); reinterventions significantly more in number ($P<0.05$) and reinfection more frequent ($P<0.01$) in PI group (9 cases vs. 1 case); no difference was seen in AE rates; both low/safe
	Evaluation of HOCl/silicone gel vs. a branded silicone gel for hypertrophic scars and keloids (n=40);[25] study not powered for statistical superiority between products (trend analysis possible)	Double-blind, randomized study with TID application of study gel for 8wks (56 days); qualified scars were widespread hypertrophic scars and keloids present for 3–12mos; evaluations at Days 14, 28, 56, 84, and 112 using VSS and symptom scores performed; IGA score and subject satisfaction data at Day 56 (end of therapy) and at Day 112 (end of study) collected	Individual scores for pain and pruritus decreased (improved) in both groups over course of study; mean reduction of scores greater in HOCl/silicone group; IGA assessment ratings at Days 56 and 112 very good/good in 6 and 11 subjects in HOCl/silicone group and in 5 and 5 subjects in silicone group, respectively; trends showed superiority in HOCl/silicone group; no major AEs noted in either group

HOCl: Hypochlorous acid; AD: atopic dermatitis; BID: twice daily; MRSA: methicillin-resistant Staphylococcus aureus; MBC: minimum bactericidal concentration; HSV: herpes simplex virus; IGA: Investigator Global Assessment; SGA: Subject Global Assessment; PGA: Participant Global Assessment; PRN: when necessary; VAS: Visual Analog Scale; BP: benzoyl peroxide ; PI: povidone iodine; TID: 3 times daily; AE: adverse event; VSS: Vancouver Scar Scale

Dermatology Conference 2017. Las Vegas, Nevada; 12–15 Oct 2017.
14. Piaggesi A, Goretti C, Mazzurco S, et al. A randomized controlled trial to examine the efficacy and safety of a new super-oxidized solution for management of wide postsurgical lesions of the diabetic foot. *Int J Lower Extr Wounds.* 2010;9(1):10–15.
15. Dalla Paola L, Brocco E, Senesi A, et al. Super-oxidized solution (SOS) for infected diabetic foot ulcers. *Wounds.* 2006;18(9):262–270.
16. Totoraitis K, Cohen JI, Friedman A. Topical approaches to improve surgical outcomes and wound healing: a review of efficacy and safety. *J Drugs Dermatol.* 2017;16(3):209–212.
17. Friedman AJ, Cash K, Berman B. Hypochlorous acid is anti-inflammatory and immunomodulatory. Poster presented at the Winter Clinical Dermatology Conference 2013. Kauai, Hawaii; 18 Jan 2013.
18. Tirado-Sanchez A, Ponce-Olivera RM. Efficacy and tolerance of superoxidized solution in the treatment of mild to moderate inflammatory acne: a double-blind placebo-controlled, parallel-group, randomized, clinical trial. *J Dermatol Treat.* 2009;20(5):289–292.
19. Duc QI, Breetveld M, Middlekoop E, et al. A cytotoxic analysis of antiseptic medication on skin substitutes and autograft. *Br J Dermatol.* 2007;157(1):33–40.
20. Wang L, Bassiri M, Najafi R, et al. Hypochlorous acid as a potential wound care agent: part 1. Stabilized hypochlorous acid: a component of the inorganic armamentarium of innate immunity. *J Burns Wounds.* 2007;6:e5.
21. Hostynek JJ, Wilhelm KP, Cua A, et al. Irritation factors of sodium hypochlorite solutions in human skin. *Contact Dermatitis.* 1990;23(5):316–324.
22. Oculus Innovative Sciences. Data on file.
23. Mainnemare A, Megarbane B, Soueidan A, et al. Hypochlorous acid and taurine-N-monochloramine in periodontal disease. *J Dent Res.* 2004;83(11):823–831.
24. Gold MH, Andriessen A, Dayan SH, et al. Hypochlorous acid gel technology—its impact on postprocedure treatment and scar prevention. *J Cosmet Dermatol.* 2017;16(2):162–167.
25. Bucko AD, Draelos ZD, Dubois JC, et al. Double-blind, randomized study to determine the substantial equivalence of Microcyn scar management hydrogel vs Kelo-cote scar gel for the management of hypertrophic or keloid scars. Poster presented at the Winter Clinical Dermatology Conference 2016. Koloa, Hawaii; 15–20 Jan 2016. JCAD