The Rationale Behind Topical Vitamin D Analogs in the Treatment of Psoriasis

Where Does Topical Calcitriol Fit In?

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Topical vitamin D analogs have become an integral component of the armamentarium used for the treatment of psoriasis. Clinical experience and multiple studies with topical vitamin D analogs have demonstrated efficacy with both monotherapy and combination therapy, with the latter approach found to be more applicable in the clinical setting. The most recent of this class of agents released in the United States is calcitriol. Calcitriol is a natural topical vitamin D3 analog with both short- and long-term studies demonstrating its efficacy and safety, with minimal risk of side effects.[1,2] Studies have confirmed its efficacy as monotherapy; however, this agent is also applicable to combination therapy for psoriasis, providing a "corticosteroid-sparing" benefit with a reduction in side effects and a decrease in relapse rates.[3] The following review provides an overview of psoriasis management, with a focus on the use of topical therapy, and examines the evolution of calcitriol ointment in psoriasis treatment. Emphasis is placed primarily on the management of chronic plaque psoriasis.

What are some important general considerations regarding psoriasis as a disease state?

Psoriasis is a chronic and incurable inflammatory skin disease, affecting 2 to 3 percent of the United States population, which may vary in severity from mild and localized to severe and diffuse.[4] The most commonly encountered clinical subtype of psoriasis is chronic plaque psoriasis (CPP), also referred to as psoriasis vulgaris. Overall, psoriasis appears to be most common among the Caucasian population and has been reported to be more widespread in places of higher latitudes.[4] Psoriasis can have a significant impact on quality of life (QOL), and is comparable to other major medical conditions in adversely affecting many QOL parameters.[5–7] The cost of care for psoriasis patients for hospitalization, outpatient physician visits, phototherapy, prescription therapies, and over-the-counter medications has been estimated to be $649.6 million per year.[8] Psoriasis patients can experience considerable discomfort with inflammation, infection, soreness, and burning.[9] Despite the availability of several topical and systemic therapies, the chronicity and relapsing nature of the disorder is a major psychosocial and physical burden to many affected individuals, and is a major therapeutic challenge for even the most knowledgeable and astute clinicians.

What is the status of topical therapy in the management of chronic plaque psoriasis?

Topical corticosteroids have long been considered the first line of therapy for CPP. These agents offer substantial improvement within the first month of use, especially with formulations of higher potency. The difficulties encountered with topical corticosteroid therapy include adverse reactions associated with prolonged continuous use and tachyphylaxis. Tachyphylaxis describes a reduced therapeutic effect despite continued application, which may be due to a true loss of efficacy, poor adherence, or both. Nevertheless, despite the therapeutic importance of topical corticosteroids in the treatment of psoriasis, it is important that clinicians modify their use and incorporate other therapeutic approaches to reduce side effects and optimize efficacy. Among other topical options, vitamin D analogs are commonly used alternatives, often as monotherapy in cases of intertriginous or flexural psoriasis, and in combination with topical corticosteroids, systemic therapies, and phototherapy, in patients with CPP.[10,11]

Topical therapy is an important component in long-term maintenance therapy of CPP when attempting to

sustain long-term remission. A recent study of US dermatologists reported that 86 percent of all patients with psoriasis receive topical therapy.[12] To add, topical therapy is not always reserved for patients with mild disease and may be used adjunctively with systemic medications, such as biologic agents.[13] Although topical corticosteroids are incorporated as initial therapy and can produce rapid improvement in signs and symptoms, long-term use is complicated by the potential for cutaneous atrophy, striae, persistent erythema, and telangiectasia.[13,14] A potential systemic effect associated with prolonged topical corticosteroid use is suppression of the hypothalamic-pituitary-adrenal (HPA) axis, which is not often of clinical relevance as the agent is usually discontinued or tapered to intermittent use. However, HPA axis suppression may be clinically significant in some cases when a topical corticosteroid is used on large body surface areas (BSAs) over a prolonged duration, especially with higher potency agents.[14,15]

In a questionnaire-based study of 200 patients with atopic eczema, 72.5 percent of patients were concerned with using topical corticosteroids.[16] Nearly 25 percent of the patients also replied that they were nonadherent with treatment due to their concern over side effects.[16] Although these patients had symptomatic eczematous dermatitis, corticosteroid side effects ("steroid phobia") are often a concern of patients. Although "steroid phobia" may be an exaggerated concern when use of topical corticosteroids is supervised and monitored by a competent clinician, such patient concerns can translate into nonadherence even in psoriasis patients, especially due to the chronic nature of the disease.

The introduction of topical vitamin D analogs provides the advantage of "steroid-sparing" effects and a favorable safety profile. This is reflected in one study in which compliance was slightly higher with topical vitamin D analogs (57%) compared to topical corticosteroids (50%) with patients being less concerned with more prolonged use of a vitamin D agent.[17] In addition, inappropriate use of topical corticosteroids on a chronic basis is also a concern to the clinician. The risk of cutaneous adverse events is high when corticosteroids are applied to sensitive skin areas, such as the face or intertriginous regions.[18] Therefore, the optimal topical treatment regimen for psoriasis is based on data supporting efficacy, long-term safety, and avoidance of adverse effects, as fear of side effects among patients can reduce adherence.[19]

What are the potential correlations between vitamin D and psoriasis?

Psoriasis is an immune-mediated disease, with T cells and cytokines involved as the primary effectors of inflammation. In psoriatic lesions, keratinocytes proliferate and mature at an extremely fast rate leading to incomplete terminal differentiation. Studies have found that vitamin D analogs contribute to the normalization of keratinocyte hyperproliferation.[20] In recent years, the role of vitamin D analogs in regulating the immune system has become more clear. Vitamin D is both a vitamin and a hormone with physiological activity affecting both serum calcium and phosphorus levels.[11]

Vitamin D_3 acts mainly on the vitamin D receptor (VDR) to regulate cell growth, differentiation, and immune function as well as calcium and phosphorus metabolism.[11] Vitamin D_3 also inhibits production of interleukin-2 (IL-2) and IL-6, blocks transcription of interferon (IFN)-gamma and granulocyte-macrophage colony-stimulating factor (GM-CSF) messenger ribonucleic acid (mRNA), and inhibits cytotoxic T cells and natural killer cell activity.[21] Vitamin D_3 also inhibits proliferation of keratinocytes in culture and modulates epidermal differentiation.[11] VDR binds to and activates transcription of vitamin D responsive genes.[13] Experimental studies have shown that calcitriol specifically has immunomodulatory effects on monocytes, macrophages, T cells, and dendritic cells.[20]

The therapeutic use of vitamin D dates back to the 1930s when it was used as an oral agent for osteoporosis on a psoriasis patient who subsequently experienced clearing of psoriatic skin lesions.[10] Dermatological application of topical vitamin D_3 centers on the fact that the skin is both a site of initial vitamin D biosynthesis and a target for vitamin D_3 activity causing modulation of keratinocytes and inflammatory mediators.[11]

What are the currently available vitamin D analogs available in the United States?

At present, the two vitamin D analogs available in the Unites States, both analogs of vitamin D_3, are calcipotriene and calcitriol.

Calcipotriene. Vitamin D_3 analogs have become a major part of treatment for CPP. They are more efficacious and exhibit superior cosmetic acceptability as compared to older topical treatments, such as tar and dithranol, and have been shown to exhibit potency comparable to mid-potency topical corticosteroids.[22] The synthetic vitamin D_3 analog calcipotriene has been available in the

United States since 1994.[19] Calcipotriene was first approved in the early 1990s in Europe as a 0.005% ointment formulation under the generic name of calcipotriol.[23] Calcipotriene is a synthetic analog of vitamin D and is one of the most commonly prescribed medications for the treatment of psoriasis.[24] Calcipotriene was also the first vitamin D_3 analog to be used in psoriasis. One of the adverse events associated with calcipotriene is cutaneous irritation, observed in up to 20 percent of patients, especially when applied to the intertriginous areas or to the face.[25] Subsequently, calcitriol and tacalcitol were developed as were maxacalcitol and tisocalcitate more recently.[22] Tacalcitol is not available in the United States. Although reported to be less irritating than calcipotriene, tacalcitol may also be less efficacious.[22,25–27]

Calcipotriene as monotherapy has been shown to improve signs and symptoms in approximately 60 to 70 percent of patients with CPP with maximum efficacy observed at Weeks 6 to 8.[28] Based on both short- and long-term data, calcipotriene has proven to be efficacious and safe.[11,29] In trials in which calcipotriene was compared with anthralin, it fared well in terms of clinical efficacy and was preferred by patients because it did not stain and was less irritating.[30] Calcipotriene is associated with cutaneous irritation in approximately 20 percent of patients and is not consistently suitable for application to the face.[26] Calcipotriene use has not been commonly associated with clinically significant hypercalcemia, possibly because it is rapidly metabolized after topical application.[11] After the advent of a combination product containing calcipotriene and betamethasone dipropionate ointment, calcipotriene is available as a cream; however, the ointment is no longer commercially available as an individual product in the United States.[31,32]

Calcitriol. Topical calcitriol ointment (3µg/g) is the only vitamin D_3 analog available as an ointment in the United States. It has comparable efficacy and favorable tolerability when compared to other topical vitamin D_3 analogs and is now widely used. Calcitriol ointment is approved for the treatment of mild-to-moderate plaque psoriasis in patients aged 18 years or older.[33] Calcitriol ointment has good patient-rated spreadability and is also cosmetically acceptable.[32] It should be applied twice daily, morning and evening to affected areas. It is also less irritating compared to calcipotriene and may be applied to the face and the intertriginous zones with less irritation.[33] Calcitriol ointment has excellent efficacy, safety, and tolerability, and will be discussed in more detail.[33]

What are the results of short-term clinical trials of topical calcitriol used for treatment of psoriasis?

Calcitriol was evaluated in a double-blind, parallel-group, vehicle-controlled, dose-ranging study that examined four different doses of calcitriol ointment (range 0.3–9.0µg/g) in 245 patients with CPP.[1] Global improvement of psoriasis was markedly higher among 71 percent of patients in the 3µg/g group, 77 percent in the 9µg/g group, and 46 percent in the vehicle group after Week 8.[1] The dose of 3µg/g was found to be the minimum concentration of topical calcitriol needed for clinical efficacy and was comparable to higher doses.[1] None of the patients developed significant hypercalcemia, elevated plasma calcitriol concentrations, serum albumin-adjusted calcium, serum phosphorus, urinary calcium, or urinary phosphorus in this study.[34]

The efficacy and safety of topical calcitriol ointment applied twice daily were examined in two identically designed, placebo-controlled, randomized, multicenter, parallel-group, eight-week clinical trials in subjects more than 12 years of age with CPP.[35] Approximately three-fourths of subjects in both the topical calcitriol-treated (n=419) and vehicle groups (n=420) presented with CPP of moderate severity, with a baseline affected BSA of 10.3 percent in the calcitriol group and 10.8 percent in the vehicle group. In the first study, the percentage of patients reaching the Global Severity Score (GSS) endpoint of treatment success, defined as "clear" or "minimal" disease, was 34.4 percent in the calcitriol group and 22.5 percent in the vehicle group (P=0.005).[1] The second study revealed that the percentage of patients reaching the GSS endpoint of treatment success was significantly better for calcitriol (33.3%) compared to vehicle (12.3%) (P<0.001).[35] The incidence of adverse events were similar in both study arms for Study 1 and Study 2, reported as 6.7 percent and 10.5 percent in the calcitriol groups and 9.6 percent and 11.8 percent in the vehicle groups, respectively.[35] Treatment-related adverse events included skin discomfort, pruritus, and erythema, which were predominantly mild.[35]

What are the results of long-term clinical trials of topical calcitriol used for treatment of psoriasis?

Ideally, successful topical therapy for psoriasis incorporates favorable efficacy, tolerability, and overall safety based on study data and clinical

experience with short-term and long-term usage. Studies suggest that in "real-world" clinical practice, topical vitamin D formulations are appropriate for use in a variety of combination therapy regimens for patients with CPP and may also be utilized as monotherapy where clinically applicable. Importantly, there are data supporting efficacy and safety with prolonged application of calcitriol ointment twice daily in patients with psoriasis. Two long-term, prospective, clinical trials studying the efficacy and safety of twice-daily application of calcitriol ointment 3µg/g for one year or longer have been completed.[2,23]

The first study was an open-label, multicenter, prospective, clinical trial in patients (N=257) with CPP treated for three or more months, and up to a maximum of 18 months.[2] The mean Psoriasis Area Severity Index (PASI) score decreased by 53 percent over the initial three months of active treatment, from 9.71 at baseline to 4.24 after use of calcitriol ointment twice daily.[2] The PASI scores remained approximately 50 to 60 percent below baseline values throughout the study duration, with 219 subjects treated for three or more months, 149 subjects treated for six or more months, 75 subjects treated for 12 or more months, and 16 subjects treated for 18 months.[2] No statistically significant differences or clinically significant changes were observed between baseline and post-treatment for any laboratory values, including calcium and phosphorus.[2]

The second prospective clinical trial was conducted to further establish the long-term safety and efficacy of calcitriol ointment in a large patient population.[36] This was an open-label, single-group study designed such that at least 100 study subjects would complete 12 months of therapy with calcitriol ointment applied twice daily. A total of 324 subjects with CPP were enrolled in 30 centers in Europe with an affected BSA of 35 percent or less.[36] The mean BSA at baseline was 16.1 percent, with baseline severity of CPP graded as moderate in 55.2 percent or severe in 25.9 percent of subjects. Treatment was completed for 180 days or more in 233 subjects, and for 52 weeks in 136 subjects. After 26 weeks of therapy (n=249), 52.6 percent of subjects were rated as at least markedly improved based on investigator assessment. In those subjects treated for 52 weeks (n=136), 63.8 percent were rated as at least markedly improved by the investigator. Overall, the mean percent BSA affected by CPP decreased from 16.1 percent at baseline to 10.7 percent at the final evaluation.[36] The results of this long-term clinical trial confirmed the favorable safety profile and efficacy of topical calcitriol 3µg/g ointment twice daily in patients with CPP.[36] Based on two long-term studies, there were no major safety signals related to prolonged application of topical calcitriol, with adverse events (AEs) similar in type and frequency to what had been previously reported in the aforementioned pivotal trials.[2,23,36]

What information was determined regarding the risk of hypercalcemia with calcitriol ointment based on long-term studies in patients with psoriasis?

There were no emergent safety concerns, including the risk of hypercalcemia, with prolonged twice-daily application of calcitriol ointment based on both long-term studies, including the larger 52-week study, which assured that at least 100 subjects were treated for 12 months.[2,23,36] Evaluation of the risk of hypercalcemia was one of the major objectives of this larger trial and was diligently assessed over the course of the study.[23,36] In this study (N=324), hypercalcemia was reported in 3.1 percent of cases, which equated to 10 individual laboratory studies occurring in nine subjects in total. All but one of the reports were single, isolated elevations of serum calcium in different subjects that occurred after varying treatment durations and were not persistent on later testing. One subject exhibited two reports of serum calcium elevation above the reported normal range; however, the rise in serum calcium was minimal. In all 10 reports of hypercalcemia, the actual elevations in serum calcium were negligible, felt to be spurious, and were determined not to be clinically relevant.[23,36] In both clinical trials and in "real-world" practice, it is important to recognize that modest, isolated elevations in laboratory test results are not uncommon, are fully anticipated, and are often clinically irrelevant; however, marked and/or persistent elevations may be clinically significant. Fortunately, no marked or persistent elevations in serum calcium levels were observed with prolonged application of calcitriol ointment in patients with CPP, including subjects with an affected BSA range of 25 to 35 percent (n=71).[36]

What comparative trials have been completed with calcitriol ointment?

A multicenter clinical trial compared the cutaneous safety and efficacy of calcitriol (3µg/g) ointment and calcipotriene (50µg/g) ointment in patients (N=75) with mild-to-moderate CPP affecting sensitive skin areas, such as the face, hairline, retroauricular folds, and flexural areas.[37] This was a double-blind, intra-individual design in which patients

with bilateral and symmetrical psoriasis lesions that were similar in severity on both sides consistently applied calcitriol ointment twice daily on one side and calcipotriene ointment twice daily on the opposite side. Global assessment of improvement was significantly greater with calcitriol than with calcipotriene ($P<0.02$), which was primarily attributable to greater improvement of flexural areas treated with calcitriol. Tolerability was rated as excellent for 24 of 30 patients (80%) with flexural lesions treated with calcitriol versus 17 of 30 patients (57%) treated with calcipotriene.[37] Of the 56 patients with retroauricular lesions, tolerability at these sites was rated as excellent for 35 patients (62%) treated with calcitriol and for 21 patients (38%) treated with calcipotriene.[37] With regard to overall tolerability, the calcitriol side was rated significantly better by 37 of 75 patients (49.3%) compared to 8 of 75 patients (10.7%) in the calcipotriene group ($P<0.0001$).[37] Based on this study of psoriasis treatment involving "more sensitive" anatomic locations, calcitriol ointment was more effective than calcipotriene ointment, primarily in flexural areas, and was associated with less cutaneous irritation.[37]

Another study compared calcitriol (3µg/g) ointment to a high potency topical corticosteroid, betamethasone dipropionate (0.05%) ointment.[38] Patients (N=250) with moderately severe CPP were randomized into a double-blind treatment group with calcitriol ointment or betamethasone dipropionate ointment for six weeks.[38] The mean severity score after treatment was 1.58 for the calcitriol group and 1.36 for the betamethasone group favoring betamethasone dipropionate ($P<0.05$).[38] The mean PASI score decreased from 15.7 at baseline to 5.4 after six weeks in the calcitriol group and from 15.02 to 3.67 in the betamethasone dipropionate group, with the difference between groups not statistically significant.[38] Patients in the calcitriol group (48%) were significantly more likely than were those in the betamethasone dipropionate group (25%) to remain free of relapse of CPP during eight weeks of post-treatment follow up ($P<0.01$).[38] The rate of remission following discontinuation of treatment was nearly twice as great in the calcitriol group as compared to the betamethasone dipropionate group (48% versus 25%).[38]

How might calcitriol ointment be used in combination with other therapies?

When considering a topical agent for CPP it is important to assess how it will fare in combination with other treatments since many patients require more than one agent to achieve and/or sustain control of CPP. One study examined the efficacy and safety of calcitriol ointment in combination with ultraviolet B (UVB) phototherapy.[39] The authors noted that combination therapy may reduce UVB exposure and as a result decrease the risk of carcinogenic side effects. A randomized, double-blind, multicenter clinical trial compared the efficacy and safety of UVB phototherapy in combination with calcitriol ointment compared to UVB phototherapy alone in patients with moderate-to-severe CPP (N=104).[39] Study subjects applied either calcitriol (3µg/g) ointment or vehicle ointment twice daily for up to eight weeks, and all of them underwent a maximum of 24 UVB sessions. The addition of calcitriol ointment resulted in significantly greater improvement than UVB alone, with results noted as early as the first week ($P<0.05$).[39] Change in CPP was rated as improved or cleared for 45 percent of subjects who received UVB and calcitriol versus 20 percent of subjects who received UVB alone ($P<0.05$).[39] Both treatments were well tolerated and produced similar rates of treatment-related AEs.[39] Because of the greater clinical response in the calcitriol group, subjects in this active combination arm required fewer UVB treatments and received 34 percent less UVB radiation exposure than did subjects in the vehicle group.[39] This is advantageous as UV irradiation carries carcinogenic risks, especially in patients treated chronically with phototherapy.

The combination of a topical corticosteroid and a topical vitamin D3 formulation is rational for several potential reasons, including the incorporation of different modes of action, augmented therapeutic benefit, and reduction in side effects.[40] Corticosteroids are thought to improve psoriasis through a myriad of anti-inflammatory and immunosuppressive mechanisms, and vitamin D_3 agents through reduction in keratinocyte proliferation and their own inherent anti-inflammatory activities.[41] Topical vitamin D_3 therapy allows for reduction in the frequency of corticosteroid application, and hence lowers the risk of AEs, including local cutaneous reactions, such as atrophy and striae. In addition, cutaneous irritation, which may be caused in some cases with topical vitamin D3 therapy, may be alleviated to some degree by the anti-inflammatory effects of a topical corticosteroid.[41] Clinical studies have revealed that topical vitamin D_3 therapy has been shown to extend the duration of remission when added to topical corticosteroid treatment.[3]

Another study examined the efficacy and safety of calcitriol

ointment in combination with betamethasone valerate 0.1% ointment.[42] In a small, randomized, double-blind study, patients were treated with betamethasone valerate ointment each morning and evening (n=10), or with betamethasone valerate ointment each morning and calcitriol (3µg/g) ointment each evening (n=9).[41] The mean PASI score decreased from baseline to 81 percent for patients in the calcitriol plus betamethasone valerate group and by 75 percent in the betamethasone valerate only group.[42] These pilot results suggest the possibility that substitution of calcitriol ointment for once-daily application of betamethasone valerate is as effective as twice-daily application of betamethasone valerate. However, no statistical analysis of outcomes was performed, and betamethasone valerate ointment once daily was not evaluated. Nevertheless, combination therapy with a topical corticosteroid of adequate potency to treat CPP and a topical vitamin D_3 agent can result in more favorable efficacy, greater safety related to corticosteroid-induced side effects and reduced skin irritation, and incorporation of maintenance therapy regimens with intermittent topical corticosteroid use, as compared to topical monotherapy.[13]

What additional data is available on safety and tolerability of topical calcitriol?

Oral calcitriol stimulates both the absorption of calcium from the gastrointestinal tract and the mobilization of calcium from bones, resulting in elevation of serum calcium levels.[28] Hypercalcemia has been raised as a concern when using topical vitamin D analogs, including calcitriol, especially with repeated application to a large BSA. A pharmacokinetic study incorporating a maximum topical dose of calcitriol (3µg/g) ointment, allowing for application on up to 35-percent BSA twice daily for 21 days, examined use in patients with CPP.[43] A subset of 152 patients from both Phase 3 calcitriol ointment studies underwent extensive laboratory testing for a number of measures that assessed calcium homeostasis. Laboratory values included serum total calcium, albumin-adjusted calcium, 24-hour urinary calcium, phosphorus, creatinine clearance, and urinary calcium to creatinine ratio.[35] Topical calcitriol did not significantly alter the mean values of any of these laboratory measurements. None of the serum calcium values exceeded levels of 10 percent above the upper limit of normal, and all but one of the results were less than five percent above the upper limit of normal.[35] Routine monitoring of serum calcium levels is not generally recommended; however, the clinician may always choose to monitor in selected cases, especially when widespread prolonged application is used, or if there is an underlying medical condition that may predispose to hypercalcemia. For patients who develop marked hypercalcemia while using topical vitamin D therapy, treatment should be discontinued until laboratory measurements reflecting calcium levels and metabolism have returned to normal.[44]

Evaluation of safety parameters including cumulative irritancy, cutaneous contact sensitization, potential photoallergic contact sensitization, and phototoxicity demonstrated excellent safety and tolerability of calcitriol (3µg/g) ointment.[45] Cutaneous irritancy was evaluated through a single-center, randomized, vehicle-controlled, evaluator-blinded, intra-individual comparison.[45] The cutaneous tolerability of calcitriol was found to be better than that of calcipotriene. Calcitriol did not give rise to sensitization, and when compared to its vehicle and white petrolatum it demonstrated no potential photoallergic contact sensitization or phototoxicity.[45] Topical calcitriol has been shown to be well tolerated with minimal side effects, even for sensitive skin areas, including continuous use up to one year.[33]

What specific cautions are suggested with the use of topical calcitriol?

The maximum recommended dose of calcitriol ointment should not exceed more than 200g per week.[43] Calcitriol ointment should not be used for oral, ophthalmic, or intravaginal use, and has not been studied in pregnant or nursing women.[11,33]

What concluding remarks can be made about the use of topical calcitriol for psoriasis?

The efficacy and safety profile of topical treatments are key contributors to adherence in psoriasis patients. Although topical corticosteroids are the main first-line treatment, concern regarding side effects, especially with prolonged use, can negatively impact adherence in some cases. Incorporation of a "steroid-sparing" topical agent allows for the benefit of two different topical therapies, and reduces the risk of adverse effects.[46] In addition, patients may develop tachyphylaxis as a consequence of chronic topical corticosteroid therapy.[47] Due to the chronic nature of CPP, effective topical treatment is best supported by both short-term and long-term efficacy and safety data. Therefore, careful attention should be given to prescribing a regimen that is practical

and safe. Topical calcitriol has been shown to exhibit favorable efficacy and safety based on both pivotal and long-term studies, has been evaluated over a broad range of severity of CPP, and exhibits some advantages over topical calcipotriene based on comparative data.

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QUESTIONS • CHALLENGES • CONTROVERSIES