LASER RESENSITIZATION OF MEDICALLY UNRESPONSIVE NEO VASCULAR AGE-RELATED MACULAR DEGENERATION

Efficacy and Implications

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Purpose: Drug tolerance is the most common cause of treatment failure in neovascular age-related macular degeneration. “Low-intensity/high-density” subthreshold diode micropulse laser (SDM) has been reported effective for a number of retinal disorders without adverse effects. It has been proposed that SDM normalizes retinal pigment epithelial function. On this basis, it has been postulated that SDM treatment might restore responsiveness to anti-vascular endothelial growth factor drugs in drug-tolerant eyes.

Methods: Subthreshold diode micropulse laser treatment was performed in consecutive eyes unresponsive to all anti-vascular endothelial growth factor drugs, including at least three consecutive ineffective aflibercept injections. Monthly aflibercept was resumed 1 month after SDM treatment.

Results: Thirteen eyes of 12 patients, aged 73 to 97 years (average, 84 years), receiving 16 to 67 (average, 34) anti-vascular endothelial growth factor injections before SDM treatment were included and followed for 3 months to 7 months (average, 5 months) after SDM treatment. After SDM treatment and resumption of aflibercept, 92% (12 of 13) of eyes improved, with complete resolution of macular exudation in 69% (9 of 13). Visual acuity remained unchanged. Central and maximum macular thicknesses significantly improved.

Conclusion: Subthreshold diode micropulse laser treatment restored drug response in drug-tolerant eyes with neovascular age-related macular degeneration. Based on these findings, a theory of SDM action is proposed, suggesting a wider role for SDM as retinal reparative/protective therapy.

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Pharmacologic inhibitors of vascular endothelial growth factor (VEGF) have become the mainstay of treatment for neovascular age-related macular degeneration (NAMD). They are the most effective current intervention to reduce macular exudation, arrest choroidal neovascular membrane (CNVM) growth, and most importantly, reduce the risk of visual loss.1,2 Thus, ineffectiveness of anti-VEGF medication presents a serious and sight-threatening problem for which there are currently no comparably effective alternatives.

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Current intravitreal anti-VEGF medications use pharmacologic (large) doses of medication designed to temporarily remove, by binding, VEGF from the vitreous cavity, retina, and submacular space. The main source of VEGF in the retina is the retinal pigment epithelium (RPE). The causes of local regulatory dysfunction and RPE overproduction of VEGF in NAMD are complex and not fully understood. Vascular endothelial growth factor production is linked to the expression of many other factors, the absolute levels and balance of which may be altered in various disease states, and in response to various treatments, including drugs and retinal laser treatment.3

Anti-VEGF injections, typically administered on a near-monthly basis for years, may lose effectiveness with repeated use. Use of higher dosages may restore
or improve effectiveness in some cases. The gradual loss of drug effect that may, at times, respond to an increased drug dosing is termed drug “tolerance.” Drug tolerance is generally a permanent condition. This is distinguished from “tachyphylaxis,” in which the loss of drug response tends to develop almost immediately, is not dose dependent, but may also resolve after a period of abstinence. Therefore, “tolerance” seems to best describe the typical loss of response to anti-VEGF drugs in the treatment of NAMD.

Some patients who become tolerant to one anti-VEGF drug will respond to a different anti-VEGF drug. However, some of these patients eventually become tolerant and unresponsive to all available anti-VEGF medications. Verteporfin photodynamic therapy has been reported to be beneficial as “rescue therapy” in such cases. Generally, however, the loss of anti-VEGF monotherapy effectiveness bodes ill for the visual prognosis.

“High-density/low-intensity” subthreshold diode micropulse laser (SDM) treatment was first reported in 2005. By definition, SDM does not cause retinal damage and has no known adverse treatment effect. Subthreshold diode micropulse laser has been reported to be an effective treatment in a number of retinal disorders, including diabetic macular edema (DME), proliferative diabetic retinopathy (DR), macular edema as a result of branch retinal vein occlusion, and central serous chorioretinopathy. The safety of SDM is such that it may be used transfoveally in eyes with 20/20 visual acuity to reduce the risk of visual loss caused by early fovea-involving DME.

It has been suggested that SDM works by targeting, preserving, and “normalizing” (moving toward normal) the function of the RPE. Tolerance to anti-VEGF medication appears to develop via drug-induced disturbance of RPE autoregulation, resulting in altered cytokine expression. By defining “normal” in this setting as the state of the RPE initially responsive to drug therapy, we hoped that SDM treatment might reverse drug tolerance by restoring drug sensitivity in eyes with NAMD no longer responsive to anti-VEGF therapy. In the following, we report our experience using SDM to restore drug sensitivity in a small group of eyes with drug-tolerant NAMD and discuss the implications of our findings.

Methods

With approval of an investigational review board and adhering to the tenets of the Declaration of Helsinki, the records of all patients treated for NAMD in a private vitreoretinal subspecialty practice were reviewed. Inclusion criteria included the diagnosis of NAMD requiring intravitreal injections of anti-VEGF medication; initial medication effectiveness; development of drug nonresponse, defined as persistence or worsening of subretinal fluid (SRF) and/or cystoid macular edema (CME) by spectral-domain optical coherence tomography despite at least 4 consecutive anti-VEGF injections given for more than 4 months to 6 months, including at least 3 final consecutive injections of aflibercept given 4 weeks to 6 weeks apart; receipt of SDM treatment after diagnosis of drug tolerance; resumption of aflibercept 1 month after a single treatment session of SDM; and at least 2 months of follow-up after SDM treatment. Exclusion criteria included other obfuscating ocular disease, including subretinal or sub-RPE hemorrhage.

Subthreshold Diode Micropulse Laser Treatment

One month after the final clinically ineffective aflibercept injection, SDM treatment was performed. After informed consent and pupillary dilation, topical proparacaine was applied to the patient’s cornea. A Mainster macular contact lens (magnification factor, ×1.05; Ocular Instruments, Bellevue, WA) was applied with viscoelastic solution. Confluent application of contiguous SDM spots were then placed over the entire area of the CNVM and SRF as indicated by pretreatment intravenous fluorescein angiography, optical coherence tomography, and contact lens examination. Treatment was performed transfoveally and extended slightly (approximately 300 μm) past the margins of the lesion and exudation into “dry” macula circumferentially to ensure complete treatment coverage. Effort was made to focus the laser on the RPE beneath the SRF and/or CME, including any underlying serous retinal pigment epithelium detachment (PED), if present. Laser parameters included the use of an 810 nm micropulsed diode laser (Oculight SLx; Iridex, Corp, Mountain View, CA) with a 300-μm aerial spot, 2.0 watt power, 5% micropulse duty cycle, and 0.20 seconds exposure duration. Treatment generally used application of at least 400 to 1,200 spots (approximately 200–300 spots per disk diameter), depending on the area to be covered (Figure 1).

Recorded data included patient demographics (age at SDM treatment, eye, and sex), pre-SDM treatment (number and type of anti-VEGF medications, photodynamic therapy), clinical measures before and after SDM treatment (visual acuity, subjective assessment of the presence, absence, improvement, or worsening of SRF, CME, and PED, maximum macular thickness [MMT] by optical coherence tomography, and central
foveal thickness), and post-SDM measures (number and frequency of aflibercept injections and any complications of treatment).

Statistical Methods

Patient characteristics and clinical measures were summarized with means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Pre-SDM to post-SDM comparisons of MMT and central foveal thickness were performed using Wilcoxon’s signed-rank test. Subjective assessment of SRF, CME, and PED over follow-up was summarized descriptively. Visual acuity was converted to logarithm of the minimum angle of resolution equivalent for analysis. SAS Version 9.3 was used for all statistical analyses.

Results

Thirteen eyes of 12 patients were included for study (Table 1). Subjects averaged 84 years old at the time of SDM treatment (range, 73–97 years). Average follow-up after SDM treatment was 5 months (range, 3–7 months). Before SDM treatment, these eyes received 16 to 67 (average, 34) intravitreal anti-VEGF injections for NAMD. Exudation unresponsive to drug treatment before SDM included SRF alone in 9 eyes (69%), CME and SRF in 2 eyes (15%), and CME alone in 2 eyes (15%). Before SDM treatment, 6 eyes (46%) had concurrent PED. The average pre-SDM central foveal thickness was 349 μm (standard deviation = 102 μm), average pre-SDM MMT was 435 μm (standard deviation = 111 μm), and average visual acuity in logarithm of the minimum angle of resolution equivalent was 0.33 (standard deviation = 0.11).

Comparisons between pre-SDM and post-SDM measures are displayed in Table 2. Central foveal thickness showed significant reductions at 3, 4, and 5 months post-SDM compared with pre-SDM (decreases of 67, 93, and 103 μm, respectively; all $P \leq 0.0605$). Central foveal thickness measured at 2 months to 5 months after SDM treatment, after reinjection of aflibercept, significantly improved compared with central foveal thickness 1 month after SDM treatment and before reinjection.

Table 1. Demographics

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th>Mean (SD)</th>
<th>Minimum, Maximum</th>
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<tbody>
<tr>
<td>Age at SDM (years)*</td>
<td>84.3 (6.6)</td>
<td>73.0, 97.0</td>
</tr>
<tr>
<td>Follow-up (months)*</td>
<td>4.9 (1.4)</td>
<td>3.0, 7.0</td>
</tr>
<tr>
<td>Pre-SDM CFT†</td>
<td>349 (102)</td>
<td>189, 565</td>
</tr>
<tr>
<td>Pre-SDM MMT†</td>
<td>435 (111)</td>
<td>299, 664</td>
</tr>
<tr>
<td>Pre-SDM logMAR VA†</td>
<td>0.33 (0.11)</td>
<td>0.18, 0.48</td>
</tr>
<tr>
<td>Pre-SDM anti-VEGF injections†</td>
<td>33.8 (14.6)</td>
<td>16.0, 67.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>Frequency (Percent)</th>
</tr>
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<tbody>
<tr>
<td>Male*</td>
<td>—</td>
</tr>
<tr>
<td>White*</td>
<td>—</td>
</tr>
<tr>
<td>Pre-SDM CME†</td>
<td>4 (30.8)</td>
</tr>
<tr>
<td>Pre-SDM SRF†</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td>Pre-SDM PED†</td>
<td>6 (46.2)</td>
</tr>
</tbody>
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*Person based (n = 12 subjects).
†Eye based (n = 13 eyes).
(decreased between 61 and 95 μm; all \( P \leq 0.0391 \)). Maximum macular thickness showed similar improvement from pre-SDM and 1-month post-SDM measures. Specifically, MMT showed a marginally significant improvement of 41 μm at 2 months post-SDM \( (P = 0.0640) \), and significant improvements of 65, 103, and 105 μm at 3, 4, and 5 months post-SDM, respectively, compared with pre-SDM (all \( P \leq 0.0327 \)). In addition, MMT showed significant reductions post-SDM and after re-injection of aflibercept compared with 1-month post-SDM, which was before re-injection (all \( P \leq 0.0547 \)). No eye showed any effect from SDM alone before rechallenge with aflibercept.

Overall, visual acuity showed no significant pre-SDM to post-SDM differences. Overall, 12 of 13 eyes (92%) improved, with complete resolution of macular exudation in 9 of 13 eyes (69%). In the remaining 3 improved eyes, only trace exudation remained (Figures 2–4). Chronic PED improved or resolved in 3 of 6 eyes (50%). One eye did not respond to SDM treatment. This eye uniquely had confluent submacular pigment atrophy by fundus autofluorescence photography (Figure 5). All eyes that showed improvement after SDM treatment continued to be responsive to aflibercept throughout follow-up. There were no adverse treatment effects as a result of SDM.

### Discussion

Tolerance, or acquired loss of drug response, is a common condition that can develop to different drugs, in different cell types, in different ways. When tolerance develops to one drug, cross-tolerance to drugs of the same family is often also observed. Tolerance may be partial, or complete, and can have grave prognostic implications.\(^4\,^5\,^12\) Drug tolerance is generally permanent. To our knowledge, this is the first report of clinically effective reversal of drug tolerance in humans.\(^4\,^5\,^10\) Our findings suggest a role for SDM in the management of drug-tolerant NAMD, and by extension, as a possible adjunct to uncomplicated pharmacotherapy to optimize treatment response and minimize the injection burden. The precipitous resolution of macular exudation after SDM treatment and rechallenge with aflibercept, typical for drug response but uncharacteristic of SDM treatment alone, supports the study hypothesis, suggesting restoration of drug response in drug-tolerant NAMD eyes as the principal SDM effect.\(^8\)

Our use of SDM in these cases of medically tolerant NAMD was informed by our understanding of the general mode of action of SDM in the treatment of other disorders, such as DME. By exclusion, SDM appears to normalize RPE function.\(^6\,^9\,^13\) Thus, we used a standard set of SDM parameters for macular treatment, which was known to be clinically effective without causing laser-induced retinal damage.\(^6\) By the same token, the SDM treatment technique of placing confluent and contiguous SDM spots over the entire area of pathologic examination is informed by our hypothesis that the effects of low-intensity SDM on the RPE are amplified and the clinical effect maximized by high-density treatment application intended to recruit all of the RPE in the diseased area.\(^6\,^9\,^13\,^14\)
Fig. 2. Spectral-domain optical coherence tomography series demonstrating the resolution of macular fluid after SDM reversal of tolerance to anti-VEGF medication in NAMD. Treatment before SDM included injections of intravitreal bevacizumab (8), then ranibizumab (7), and finally aflibercept (9). A. Left eye 1 month before SDM treatment. Multifocal serous PEDs and subretinal fluid unresponsive to anti-VEGF medications were noted. Aflibercept injection repeated. B. One month later, persistence of subretinal fluid despite continued aflibercept treatment. Anti-VEGF medication tolerance diagnosed, and SDM treatment was performed. C. Two months after SDM treatment and 1 month after rechallenge with aflibercept. Reduction in subretinal fluid and decreased height of PEDs were noted. D. Four months after SDM treatment and 3 months after reinstitution of monthly intravitreal aflibercept. Further reduction in macular thickness with complete resolution of subretinal fluid and a “dry” treatment response designation were noted.
Fig. 3. Spectral-domain optical coherence tomography series demonstrating the resolution of macular exudation after SDM reversal of tolerance to anti-VEGF medications in NAMD. Treatment before SDM included intravitreal injections of bevacizumab (15), ranibizumab (12), and aflibercept (15). A. Left eye 1 month before SDM treatment with persistent submacular fluid despite long-term anti-VEGF therapy. Aflibercept redministered. B. One month later, no improvement in macular exudation. Drug tolerance diagnosed. Subthreshold diode micropulse laser treatment was performed. C. One month after SDM treatment. Persistent macular exudation was noted. Intravitreal aflibercept given. D. Two months after SDM treatment and 1 month after rechallenge with intravitreal aflibercept. Complete resolution of submacular fluid constituting a “dry” treatment response designation was noted.
The success of this pilot study provides important insight into the mechanism of SDM, suggesting more specifically how SDM works, and how it is able to reverse drug tolerance in NAMD.

Normal physiologic homeostasis and disease response are mediated by trophic factors produced by immune, hematopoietic, and neural cells. These include cytokines, small proteins manifold in type and effects, and powerful locally in very small amounts. Production of any one cytokine is generally linked to others by complex autoregulatory mechanisms. The clinical effects of these factors, such as VEGF, are complex and variable, reflecting both their absolute levels and level relative to other factors. In the retina, the most important cytokine source is the RPE. Sub-threshold diode micropulse laser selectively targets the RPE.

Retinal pigment epithelium–derived cytokines play important roles in most, if not all, retinal disorders. Breakdown of RPE compensatory mechanisms and autoregulation may occur as a result of various pathologic influences, altering cytokine expression, leading to the anatomical and functional derangements characteristic of specific retinal disease states. To the extent that RPE cytokine expression is alike (such as DR and branch retinal vein occlusion), treatments targeting in-common factors tend to be effective for both disorders. Retinal disorders that are more different (such as DR and central serous chorioretinopathy) tend to exhibit different cytokine associations, and thus different responses to targeted drug therapy, such as anti-VEGF medication. Despite such differences, SDM treatment has been found to be of benefit in a number of disparate retinal disorders, including chronic metabolic disease, acute occlusive retinal vascular disease, central serous chorioretinopathy, and now drug-tolerant NAMD. Subthreshold diode micropulse laser does this without inducing any morphologic change in the RPE or causing even transient breakdown in the blood–retinal barrier. Thus, SDM causes no inflammation or loss of visual function. Because SDM is salutary in unrelated retinal disorders, it appears to exert its influence before retinal cytokine expression. Thus, SDM appears to change the behavior, and consequent cytokine production, of affected RPE cells but unharmed by SDM exposure.

Like Tolstoy’s happy families, normal cells of a type tend to be alike, whereas dysfunctional cells may be different in many different ways. However, despite a near infinite variety of possible cellular
abnormalities, cells of all types share a common and highly conserved mechanism of repair: heat shock proteins (HSPs). Heat shock proteins are elicited almost immediately, in seconds to minutes, by almost any type of cell stress or injury. In the absence of lethal injury, HSPs are extremely effective repairing and returning the viable cell toward a more normal functional state. Although HSPs are transient, generally peaking in hours and persisting for a few days, their effects may be long lasting. In addition to cell repair, HSPs reduce inflammation, a common factor in many chronic progressive retinal disorders, including DR and age-related macular degeneration.20

Retinal photocoagulation is known to both induce HSP production and alter retinal cytokine expression in surviving cells. The more sudden and severe the non-lethal cellular stress (such as laser irradiation), the more rapid and robust the HSP production. Thus, micropulsed lasers, consisting of series of repetitive thermal spikes at a very steep rate of temperature change (approximately 7°C elevation with each 100 microsecond micropulse, or 70,000°C/second), may be especially effective stimulators of HSPs production, compared to non-lethal continuous wave lasers.20–27

Laser wavelengths below 550 nm produce increasingly cytotoxic photochemical effects. At 810 nm, SDM produces photothermal, rather than photochemical, cellular stress. Thus, SDM is able to affect the RPE without damaging it. Consistent with HSP activation, SDM produces prompt clinical effects, such as rapid subjective visual improvement and improved macular sensitivity measured by microperimetry, and long-term effects, such as reduction of DME and involution of retinal neovascularization. We believe that the clinical benefits of SDM are thus produced by submorbnd photothermal RPE HSP activation. In dysfunctional RPE cells, HSP stimulation by SDM results in normalized cytokine expression and consequently improved retinal structure and function.8,9,20,21,23–33

As noted above, the therapeutic effects of this “low-intensity” laser–tissue interaction are amplified in SDM by “high-density” laser application, recruiting all the dysfunctional RPE in the targeted area, thereby maximizing the treatment effect.6 These are the defining principles of SDM. Because SDM produces therapeutic effects similar to both drugs and photocoagulation, it is clear that laser-induced retinal damage is unnecessary, and by inciting inflammation and causing loss of function, only detrimental.6–9,14,21,22,34,35

Subthreshold diode micropulse laser may cause direct but limited molecular photothermal effects, such as entropic protein unfolding and disaggregation. However, by sublethal triggering of HSP activation, the photothermal effects of SDM are therapeutically maximized. Figure 6 illustrates that SDM appears well-suited for clinically safe and effective stimulation of HSP-mediated retinal repair. We believe this to be the principal therapeutic mode of SDM action.25–29

Figure 6 illustrates the calculated therapeutic range (TR) of various lasers, from the activation threshold of the promoter gene for HSP 70 to lethal cell injury. Each color pair refers to a duty cycle of 5% (black), 15% (blue), and 100% or continuous wave (green). The log of the integral goes from negative to positive.
and crosses the x-axis at critical thresholds for HSP stimulation. For SDM, these critical thresholds are 0.9 watts for HSP activation and 1.9 watts for cell death, outlining the TR of SDM (shaded area between the solid and dotted black lines). For laser parameters within this range, therapeutic benefits would be expected without lethal cell damage. For laser parameters within this and other, the ranges denoted by the shaded/colored areas, therapeutic benefits would be expected without lethal cell damage.

The Arrhenius integral is defined as 
\[
\frac{\Omega}{A} = \int \exp\left(-\frac{E}{k_B T}\right) dt,
\]
where \(A\) = a frequency factor, \(E\) = the activation energy, \(T\) = temperature, and \(t\) = time. For cell death, \(A = 10^{37}\) seconds\(^{-1}\) and \(E = 228 \text{ kJ/mol}\). For HSP stimulation, \(A = 7.0 \times 10^{282}\) seconds\(^{-1}\) and \(E = 1.74 \times 10^{7}\) kJ/mol. These calculations are based on a retinal spot of 131 \(\mu m\) and exposure envelope duration of 0.20 seconds per spot application. Each color pair refers to a duty cycle of 5% – 99%.

It is interesting to note that, although SDM HSP stimulation is nonspecific with regard to the disease process, HSP mediated repair by its nature specific to the state of the dysfunction. Heat shock proteins tend to fix what is wrong, whatever that might be. We believe this accounts for the observed effectiveness of SDM in retinal conditions as disparate as branch retinal vein occlusion, DME, proliferative DR, central serous chorioretinopathy, and in this case, drug-tolerant NAMD. Conceptually, we call this effect “reset to default.” In computer parlance, the meaning is clear: for the wide range of retinal disorders in which RPE function is critical, SDM normalizes RPE function by triggering a “reset” (back toward “normal” or the “factory default settings”) by means of HSP-mediated cellular repair. Such reparative phenomenon is not without precedent, observed with the use of laser adjuvant therapy in vaccination of immunocompromised patients and transcorneal electrical stimulation in patients with hereditary retinopathies, 3,6–9,20,21,25,28–30,34,36

Consequently, reset theory also suggests a role for SDM-triggered retinal repair and protection in other, particularly chronic and progressive, retinal diseases. The unique safety of SDM permits the use as both early preventative and maintenance therapy to prevent or slow disease progression and improve retinal function. 7–9,13,14,21,24,31–33,35–38 Just as early treatment eases management and improves final outcomes, clinical experience and reset theory suggest that SDM will be most effective before the development of disease-related anatomical degeneration, which may prevent the retina from responding to RPE autoregulatory influences. The absence of sufficient viable target RPE because of pigmentary atrophy may preclude treatment response.
(Figure 5). In addition, cells already committed to apoptosis or necrosis may be unable to respond to laser-stimulated HSP-mediated repair.13 Such factors likely account for the reduced effectiveness of all therapeutic modalities in advanced disease, again underscoring the importance of early and preventive treatment.8,9,21

No drug is always effective, and despite initial efficacy, drug tolerance may develop. Because of biologic complexity, safe and effective targeted drug therapy, like anti-VEGF medication, is difficult to develop, generally narrow in focus, and often offered late in the disease process as a result of treatment risks, adverse effects, and expense. Despite application to chronic conditions, drugs are typically short acting. Exemplified by current intravitreal anti-VEGF agents for retinal disease, drug therapy may present extraordinary burdens in terms of clinical access, social resources, and economic costs.13 Thus, despite the great benefits of pharmacotherapy, its future as a sustainable global disease management strategy for common and important diseases is necessarily limited. Such considerations underscore the need for new treatment strategies. Preventive and early treatments will offer the greatest benefits. We believe that the attributes of SDM make it uniquely suitable and promising in this regard.

Although this study is small, uncontrolled, of short duration, and involves only one clinical site and surgeon, improvement was observed in all but 1 of 13 eyes and was achieved without any adverse treatment effect. Although our findings are novel, they are also consistent with long clinical experience with the use of SDM in other retinal disorders and well-known mechanisms of laser–cell interaction and cellular repair. They suggest a possible role for the use of SDM as an adjunct to drug treatment in NAMD and a wider role for SDM-mediated retinal protection and repair. The unique safety and “reset” theory suggest that SDM may be uniquely suited for preventive treatment of important chronic progressive retinal disorders. Further study is warranted.8,9,13,31,39

Key words: micropulse laser, subthreshold, macular degeneration, neovascularization, drug tolerance, heat shock proteins, retinal protection, retinal repair, preventive treatment, early treatment, reset to default, SDM.

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References


