

## Treatment modalities of necrobiosis lipoidica: a concise systematic review

Amir Feily, Shadi Mehraban,

Department of Dermatology, Jahrom University of Medical Sciences, Iran

### Abstract

Necrobiosis lipoidica (NL) is a rare inflammatory granulomatous skin disorder closely associated with diabetes mellitus. The aim of this paper is to review and discuss all the treatment modalities proposed and tested for this disease. A systematic review of the existing literature was conducted to investigate all the available data and summarize all the clinical trials, case reports and original articles on NL. Two major databases (PubMed and Google Scholar) were used. We have examined about 70 articles. Numerous treatment modalities have been currently investigated to compare recalcitrant NL. Being rare, most of the studies regarding this disease are case reports or small-scale clinical trials. We have found that, in spite of plentiful investigations carried out during the years, there is no treatment modality that has proved to be utterly satisfactory in treating NL.

### Introduction

Necrobiosis lipoidica (NL) is a rare inflammatory granulomatous skin disorder occurring as a result of collagen degeneration.<sup>1,2</sup> Incidence rates are higher in women than men and in adults than children.<sup>3</sup> NL typically presents at 30-40 years of age.<sup>4</sup> It appears to be a discernible association between NL and diabetes mellitus (DM) in numerous studies, since Cohen *et al.* hold the view that more than fifty per cent of NL patients have concurrent diabetes; however diabetic patients also suffering from NL are less than one per cent.<sup>5</sup> Two other studies, on the other hand, regard 80 and 60 per cent of NL patients to be diabetic, respectively.<sup>1,6</sup> Regarding the substantial linkage between NL and DM and the unknown etiology of this disease, microangiopathy seems to play a notable role in the pathogenesis of NL.<sup>7</sup> It characterized by well-circumscribed erythematous plaques mostly tends to involve the tibial region of the lower extremities.<sup>8,9</sup> However, involvement of other sites of the body has also been proclaimed.<sup>7</sup> NL is a chronic relapsing-remitting disorder in which lesions are subject to ulcerations as a result of

trauma,<sup>1</sup> and it cannot always be differentiated from those of other inflammatory skin disorders.<sup>10</sup> We have gone over about seventy articles and aim to discuss all the treatment modalities proposed and tested for NL in the literature as follows (a summary is reported in Supplementary Table S1).

## Corticosteroids

### Systemic corticosteroids

Taniguchi *et al.* scrutinized the efficacy of oral corticosteroids on the NL eruptions which led to their clinical cure.<sup>11</sup> In a study of 6 patients with NL, administering systemic corticosteroids led to complete closure of all the ulcerations except for the atrophic ones.<sup>12</sup> Plus treatment with prednisolone at a dose of 6 mg/day instigated improvement.<sup>13</sup> Two other case reports of the same category, one by Tan *et al.* and the other one by Dwyer and Dick,<sup>14,15</sup> have also been published. Furthermore, Bouhanick *et al.* presented a case report in which combination therapy with local corticosteroids and hyperbaric oxygen brought about remission of NL.<sup>16</sup> Corticosteroids hereby can be regarded as an effective therapeutic agent for NL; however, their use in diabetics remains dubious considering the potential effect of destabilizing the control of DM.<sup>14</sup>

### Intralesional injection of corticosteroids

The efficacy of a Porto-jet injector with either triamcinolone acetonide or sterile normal saline was examined on five NL patients, three of which gained thorough resolution of the lesions and one only benefited from partial improvement. In spite of a high recurrence rate, reintroduction of the jet injector was advantageous.<sup>17</sup> Asteroid bodies were identified in a case of NL in which administration of dipyridamole in company with intralesional triamcinolone for two months led to the utter abrogation of the lesions, which was persistent even after the cessation of therapy.<sup>18</sup>

### Topical corticosteroids

Application of topical clobetasole propionate in two case studies proved to be effective.<sup>19</sup>

### Intravenous immunoglobulin and methylprednisolone

In a study, intravenous immunoglobulin (IVIG) showed to be effective in overcoming the recalcitrant ulcers of NL in a female patient, however reintroduction of IVIG was of less efficacy. Receiving IV methylprednisolone also provoked improvement of the lesions.<sup>20</sup>

Correspondence: Amir Feily, Department of Dermatology, Honari Clinic, Motahari Street, Jahrom, Iran.  
Tel.: +98.9177.204638.  
E-mail: dr.feily@yahoo.com

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## Pentoxifylline

The role of Pentoxifylline as a treatment modality in NL was examined on a 20-year old diabetic female with NL administered 3 times daily at a dose of 400 mg provoking improvement after one month of therapy. A 2year follow-up revealed no recurrences on top of eradicating psychosomatic pressure from the patient. No side effects of treatment were noted.<sup>21</sup> Noz *et al.* also presented a case of ulcerating NL which had failed to respond to topical and oral therapy with ASA but resolved dramatically with pentoxifylline.<sup>22</sup> The diagnosis of NL was established on the glans of the penis of a non-diabetic patient, which responded well to pentoxifylline.<sup>23</sup> Trental therapy (pentoxifylline) in 17 patients with NL demonstrated beneficial effects both in terms of correction of the hematological parameters (*e.g.* blood viscosity, red cell aggregation and stability of red cell aggregates) and developing the skin status.<sup>24</sup> Thus, pentoxifylline might be a profitable treatment option in NL. The recommended dosage is 400 mg thrice daily continued for at least 6 months.<sup>21</sup>

## Anti tumor necrosis factor-alpha therapy

### Infliximab

An investigation evaluating the effect of intralesional infliximab on 3 NL patients illustrated utter abrogation of the lesions of NL;

however, follow up after therapy revealed recurrence of the disease. No prominent side effects were noted except for the painful injections.<sup>25</sup> Also, an 84-year old type 1 diabetic woman with intractable NL illustrated marked response to the first intravenous infusion of infliximab, which led to complete clearance of the ulcers after three infusions.<sup>26</sup>

### Etanercept

Marked amelioration was noted after administration of subcutaneous etanercept in the treatment of NL.<sup>27-29</sup> However, treatment with subcutaneous adalimumab was not of any success.<sup>29</sup>

Based on the aforementioned studies, anti-TNF-alpha drugs (etanercept/infliximab) can be advantageous in challenging recalcitrant ulcerating NL by both intralesional and intravenous routes of administration; however, additional investigations are required in order to ascertain further details regarding this treatment modality (dosage and treatment duration).<sup>27</sup>

### Skin grafting

Several case reports have introduced skin grafting as a beneficial surgical intervention in severe ulcerating NL which has been applied by means of split-skin grafts and in company with porcine grafting in one case.<sup>30-33</sup> Additionally, an investigation involving 7 cases of NL in Stanford university medical center asserted split-skin grafting to be of benefit with no following recurrence.<sup>34</sup>

### Ultraviolet A1 phototherapy

Several studies have reported ultraviolet A1 (UVA1) phototherapy or topical psoralen plus ultraviolet A (PUVA) therapy to be beneficial in conquering recalcitrant NL unresponsive to other therapies, *e.g.* corticosteroids or surgery.<sup>2,35-38</sup> A 68-year old diabetic NL patient, in addition, demonstrated the same results undergoing topical PUVA therapy.<sup>39</sup>

### Cyclosporine

Administration of systemic cyclosporine-A in two different case studies demonstrated promising results.<sup>1,40</sup> Another study examining the effectiveness of cyclosporine on 2 NL patients during a 4-month period revealed complete clearance of the ulcerations which also maintained after ceasing cyclosporine

therapy.<sup>41</sup> Furthermore, a cyclosporine regimen of 2.5 mg/kg/day for recalcitrant ulcerating NL proved to be of great value; however, recurrence was determined 3 months subsequent to discontinuing therapy which regressed after resuming cyclosporine.<sup>42</sup> Smith introduced cyclosporine-A as an effective mode of treatment for NL as well.<sup>43</sup>

### Aspirin and dipyridamole (antiplatelet therapy)

A double-blind, placebo-controlled trial randomized 14 NL patients into 2 groups receiving either aspirin and dipyridamole or a matching placebo, neither of which indicated any substantial improvements.<sup>44</sup> On the contrary, the administration of acetylsalicylic acid and dipyridamole in 7 NL patients disclosed improvement of the lesions owing to diminished thromboxane levels (which were raised in all the patients prior to therapy) in the author's point of view.<sup>45</sup> In addition, Quimby *et al.* declared a low platelet survival time in NL patients extending back to normal in response to anti-platelet therapy; however, the response of the NL lesions to treatment diverged over a broad spectrum, from resolution to no perceptible improvement.<sup>46</sup> Beck and Bjerring blamed low-dose acetylsalicylic acid (ASA) therapy for a notable decline in the skin blood flow of the center of the NL lesions measured by laser Doppler technique.<sup>47</sup> Császár *et al.* proved the combination therapy of ASA and dipyridamole to be effective against the lesions of NL as well as reducing platelet aggregation.<sup>48</sup> Last but not least, a double-blind controlled study indicated enlargement of the lesions of NL following both low-dose ASA and placebo therapy.<sup>49</sup> According to the contrary outcomes of these studies, the efficacy of antiplatelet therapy remains to be seen.

### Topical tacrolimus

Barth *et al.* used topical tacrolimus ointment in the treatment of a diabetic NL patient, also a known case of protein S-deficiency and antiphospholipid syndrome which led to considerable improvement.<sup>50</sup> Another study also revealed substantial healing of the NL lesions following application of topical tacrolimus 0.1% maintaining after a 1 year follow-up.<sup>51</sup>

### Hyperbaric O<sub>2</sub> therapy

Brünger investigated the effects of 100%

oxygen on 9 non-diabetic NL patients, which brought about a significant increase in the oxygen pressure (PcO<sub>2</sub>) of the lesion, although noticeably lower than that of the normal skin as well as a dramatic upsurge in the PcCo<sub>2</sub> level of the lesion borders.<sup>52</sup> In another study, undergoing hyperbaric oxygen therapy ended up with utter clearance of all the ulcerations after 98 sessions.<sup>53</sup>

### Pancreas transplant

A retrospective study involving NL patients with DM evaluated the effectiveness of pancreas versus kidney transplant determining whether reversal of DM can result in NL resolution. Pancreas transplantation with or without a kidney transplant contributed to the resolution of the NL lesions while kidney transplant alone was not of any success.<sup>54</sup> Two case reports also described simultaneous pancreas-kidney transplant and pancreas after kidney transplant to be profitable, leaving the patient free of lesions, respectively.<sup>8,55</sup>

### Fumaric acid esters

A prospective study of 18 NL patients assessing the efficacy of fumaric acid esters (FAE) on NL demonstrated noteworthy recovery from the disease on top of an upsurge in the dermal density evaluated by 20-MHz ultrasound. After a follow up period of 6 months, no recurrences were detected, suggesting FMA as an effective medication for NL.<sup>56</sup> Also, clearance of the lesions of NL was reported in another study as a result of FMA therapy.<sup>57</sup>

### Pulsed dye laser

Pulsed dye laser was examined as a treatment approach on a 4 cm NL lesion on the anterior surface of the leg of a non-diabetic patient who received 3 sessions of therapy. The outcomes were inconclusive as the left half of the lesion demonstrated signs of resolution, whereas the right upper quadrant of the lesion indicated negligible improvement.<sup>58</sup> Furthermore, a study on a 23-year old diabetic NL patient receiving pulsed dye laser discloses this treatment modality to be ineffectual both at high and low fluencies as it could be detrimental to skin and therapeutically inconsequential, respectively.<sup>59</sup> As it can clearly be seen, pulsed dye laser doesn't appear to be a safe and an effective treatment modality for NL.

## Antimalarial agents

Nguyen *et al.* demonstrated oral chloroquine to be beneficial in confronting NL.<sup>60</sup> Also, improvement was noted after administration of antimalarial agents in 7 out of 8 patients.<sup>61</sup>

## Topical tretinoin

Heymann corroborates efficacy of topical tretinoin in overcoming the atrophic lesions of NL.<sup>62</sup> Also, favorable outcomes were achieved with the combination therapy of topical glucocorticoid and topical tretinoin in a 58-year old non diabetic female with 7 year history of NL.<sup>63</sup>

## Photodynamic therapy

Photodynamic therapy with 632 nm of red-light and methyl aminolevulinate as a topical photosensitizer showed promising results in the treatment of a 60 year-old woman with progressive NL.<sup>64</sup> However, it was effective in only 40 per cent of cases of a clinical trial.<sup>65</sup>

## Local granulocyte-macrophage colony stimulating factor

Remes and Rönnemaa examined the efficacy of GM-CSF on two diabetic patients suffering from chronic refractory NL and concluded that this treatment modality is of benefit, for improvement was noted even after the 1<sup>st</sup> episode of GM-CSF application ending in complete clearance of the lesions without recurrence after a 3-year follow-up.<sup>66</sup>

## Clofazimine

A clinical trial carried out on 10 patients suffering from NL assessed the efficacy of clofazimine administered at a daily dosage of 200 mg PO. The trial was inconclusive as the clinical response to clofazimine varied in the patients from no improvement to a thorough remission from the lesions. The side effects were both negligible and reversible.<sup>67</sup>

## PROMOGRAN

Studying the clinical efficacy of PROMOGRAN (a new protease modulating matrix)

revealed utter resolution of an ulcer of NL after 8 weeks of therapy.<sup>68</sup>

## Benzoyl peroxide

Application of 20% topical benzoyl peroxide on the ulcers of NL prompted rapid improvement of the lesions.<sup>69</sup>

## Nicotinamide

Treatment with high dose nicotinamide proved to be of efficacy in confronting NL.<sup>70</sup>

## Bovine collagen

Treatment with topical bovine collagen led to significant improvement of the lesions of NL.<sup>71</sup>

## Thalidomide

Treatment with thalidomide in a 51 year-old woman with NL left the patient free of lesions after 4 months of therapy.<sup>72</sup>

## Discussion and Conclusions

As NL is a rare disease, there are not sufficient cases to perform effective prospective clinical trials, that is why most of the experiments carried out to date are case reports and small-scale clinical trials. Plus there are few comparative studies between different treatments of NL which lead us to the conclusion that despite the introduction of all these treatment modalities for NL, the therapy of choice remains an ongoing debate requiring further large-scale studies. But to sum up, we can proclaim the introduction of corticosteroids by various routes of administration (systemic, intralesional injection and topical) as a top priority in the treatment of NL despite the possibility of destabilizing the control of blood sugar in diabetic patients.

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