

STUDY	PARTICIPANTS AND UNDERLYING DISEASE (IF APPLICABLE)	INTERVENTION(S)	FOLLOW UP	RESULTS	COMMENTS
TREATMENT WITH ISOTRETINOIN					
Balakirski 2013 [24]	Female 49 years Rosacea	Isotretinoin 30 mg/day for 1 year, then tapered to 20 mg/day for 3 months and then to 10 mg/day for 3 months (?) and then stopped	Not reported	Complete response	
Friedman 1986 [25]	Male 17 years Acne	(Previous courses antibiotics (erythromycin, tetracycline, clindamycin, minocycline, cephadrine and hydroxyzine hydrochloride 25 mg 4 times without effect) Isotretinoin 40 mg b.i.d. for 20 weeks	1 month	Estimated reduction of 50% in edema of the forehead, cheeks and upper eyelids. Acne improved dramatically after isotretinoin	The unique anti-inflammatory effect of the retinoid as reason for the beneficial effect
Garcia-Galaviz 2018 [26]	Female 19 years Rosacea	(Previous treatments with steroids, antihistamines and plasmapheresis were unsuccessful) Isotretinoin (dosage not reported)	Not reported	Objective improvement at first month follow up	
Gil 2022 [27]	Female 57 years	Isotretinoin 10 mg/day for > than 12 weeks, duration not further reported	1 year	Significant dissolution after 12 weeks, good clinical response after?	The efficacy of isotretinoin might be dependent on the degree of mast cell infiltration
Harvey 1998 [28]	Male 47 years Rosacea	(Previous treatments: corticosteroids, antibiotics unsuccessful) Isotretinoin 1 mg/kg	Not reported	Still evaluating the response to isotretinoin	
Heibel 2020 [3]	Male 24 years	Isotretinoin 40 mg/day for 3 months, then night compression therapy (facial mask) was added. 2 Months later isotretinoin dose was decreased to 40 mg every other day, for 15 months, night compression was continued	Not reported	Mild improvement after isotretinoin 3 months After 2 months isotretinoin and compression therapy, sustained significant clinical improvement during the subsequent 15 months	

Hu 2012 [29]	Male 54 years	(Previous therapies minocycline 6-7 months, short course of prednisone without effect) Isotretinoin 20 mg/day with subsequent increases up to 80 mg/day	Not reported	After 4 months isotretinoin, patient experienced improvement with decrease in erythema and edema	
Humbert 1990 [30]	1. Female 15 years Acne 2. Male 20 years Acne	1. Isotretinoin 1 mg/kg for 6 months 2. Isotretinoin 1 mg/kg for 8 months	Not reported	1. 80% improvement 2. 30-50% improvement	
Macca 2022 [31]	Male 45 years Rosacea	Isotretinoin 0.3 mg/kg/day for 6 months. Change from Continuous Positive Airway Pressure (CPAP) ventilation mask to intranasal devices	Not reported	Edema and infiltration were only slightly decreased at 6 months and isotretinoin was stopped because of lack of significant improvement and onset of side effects	Morbihan Syndrome induced by use of full-face CPAP masks for Obstructive Sleep Apnea Syndrome. Surgical treatment was proposed to debulk the enlarged tissue of lymphoedema
Manolache 2009 [32]	Male 16 years Acne	Isotretinoin 0.3 mg/kg/day for 3 months. 2 months later restarting for another 3 months (20 mg/day) because of recurrence	4 months	Remission after 3 months. Recurrence 2 months after stopping isotretinoin. Remission again after second course of isotretinoin	
Olvera-Cortés 2019 [33]	1. Male 51 years 2. Gender not reported 62 years 3. Male 29 years	1. Isotretinoin 40 mg/day for 1 year 2. Isotretinoin 40 mg/day for 1 year, then tapered to 20 mg/day for another year 3. Isotretinoin 40 mg/day for 1 year, then tapered to 20 mg/day for 6 months	1. 1 year 2. 3 years 3. Not yet	1. Complete response 2. Complete response 3. Complete response	
Singh 2020 [34]	Male 23 years	Isotretinoin 20 mg/day increased to 40 mg/day for 24 weeks	Not reported	No significant improvement	
Smith 2012 [4]	1. Male 60 years 2. Female 61 years 3. Female 46 years	1. 80 mg isotretinoin/day for 20 months 2. 40 mg isotretinoin/day for 14 months 3. 60 mg isotretinoin/day for 10 months	1. 24 months 2. 7 months 3. 4 months	Complete response in all	A substantial clinical improvement was not noted until 6 months. Starting dose of 20 mg/day, titrated up until clinical response was observed. The effective treatment dose

	4. Male 54 years 5. Female 21 years	4. 80 mg isotretinoin/day for 13 months 5. 40 mg isotretinoin/day 24 months	4. 1 months 5. 8 months		appeared to be somewhat dependent on body weight
Veraldi 2000 [35]	Male 27 years Acne	Isotretinoin 0.5 mg/kg/day for 4 months	5 years	Complete response	
Veraldi 2013 [22]	Male 60 years Rosacea	(Previous 4 years unsuccessfully treated with oral corticosteroids) Isotretinoin 0.5 mg/kg (60 mg/day) for 26 weeks	Not reported	No significant clinical improvement was observed	
TREATMENT WITH ISOTRETINOIN COMBINED WITH ANTIHISTAMINES					
Dominiak 2020 [36]	Male 45 years Rosacea	Isotretinoin 20 mg/day and ketotifen 2 mg/day for 11 months	Not reported	Significant improvement	
Jungfer 1993 [37]	Male 20 years Acne	(Previous treatment with various systemic and topical antibiotics, isotretinoin and interferon-gamma for 8 years were not effective) Isotretinoin 0.5 mg/kg/day with ketotifen 2 mg/day for 4 months	8 months	Complete response	The authors favor the clinical term <i>solid persistent facial swelling</i> (and fibrosis histologically) instead of edema, as there is no real edema
Mazzatenta 1997 [38]	Male 45 years Rosacea	Isotretinoin 0.7 mg/kg/day with ketotifen 2 mg/day for 4 months	Not reported	Lesion on the cheek had completely disappeared and the lesion on the forehead was substantially reduced	
Pastuszka 2011 [39]	Male 26 years Acne	Isotretinoin 0.5 mg/kg/day and ketotifen 1 mg b.i.d. for 9 months	Not reported	Complete response	
Rappard 2011 [40]	Female 37 years Rosacea	Isotretinoin 0.1-0.2 mg/kg/day with ketotifen 1-2 mg, for a few months	Not reported	Good effect	
Rebellato 2015 [41]	Male 38 years	(Previous minocycline and hydroxyzine for 3 months without effect) Isotretinoin 20 mg/day for 6 months with ketotifen 1 mg/day for the first 2 months	Not reported	Good clinical improvement	
Welsch 2020 [42]	4 patients (2 male/1 female/1 gender unreported)	Isotretinoin average 10 mg /day and desloratadine 5 mg/day, mean treatment duration was 14 months	Not reported	Significant reduction of erythema and edema in all	No other side effects than dryness of the lips. Not a single

	Mean age 63 years	with a minimum of 12 and a maximum of 16 months		patients. Patient satisfaction was excellent	patient needed a dose reduction nor termination of the treatment
TREATMENT WITH ISOTRETINOIN COMBINED WITH CORTICOSTEROIDS					
Cabral 2017 [43]	Male 61 years Rosacea	Isotretinoin 20 mg (0.3 mg/kg) and deflazacort (30 mg) Topical metronidazole and later oral metronidazole were added and increased dose isotretinoin to 40 mg (0.5 mg/kg) because of recurrence Reintroduction of deflazacort 30 mg/day and isotretinoin (20 mg/day)	Not reported	Excellent response after 1 month, discontinuation of corticosteroid resulted in recurrence within a few days Topical and oral metronidazole and increase of isotretinoin dose gave no improvement Reintroduction of deflazacort and isotretinoin (20 mg/day) resulted in significant improvement	Recommendation: a slow and gradual withdrawal of the medication especially the oral corticosteroid should be done
Jerković Gulin 2020 [44]	Female 30 years Acne	(Previous treatment: doxycycline 100 mg/day for 4 months unsuccessful) Isotretinoin 20 mg/day for 8 months Prednisolone 20 mg/day for 2 months tapered 3 more months	5 years	Complete regression of acne after isotretinoin, no regression of edema and erythema. Short transient improvement and rapid relapse of facial erythema and edema after prednisolone	
Lopéz 2019 [45]	Male 38 years Acne	(Previous treatment with doxycycline and prednisone showed slight improvement) Isotretinoin low dose and reduction of prednisone (dosages unknown)	Not reported	Marked clinical improvement with low dose isotretinoin and prednisone	Abstract, little information provided
Onder 2005 [46]	Male 19 years Acne	Isotretinoin 0.5 mg/kg for 2 months combined with intralesional depot corticosteroids	Not reported	Patient was satisfied with the cosmetic improvement	
Ortiz Salvador 2016 [47]	Male 16 years Acne	Isotretinoin 50 mg/day combined with prednisone 30 mg/day for 6 months	3 years	Gradual improvement but recurrence 1 month after stopping treatment, but swelling decreased slowly without treatment	

TREATMENT WITH ANTIBIOTICS					
Chaidemenos 2017 [48]	Female 63 years	Doxycycline 200 mg/day for 2 months, followed by the slowly releasing doxycycline monohydrate 40 mg/day for 6 months	51 months	Improvement after 2 months Complete response 6 months later	The sub-antimicrobial dose of 40 mg/day doxycycline monohydrate is not associated with the side effects of long-term high doses or the risk of antibiotic resistance. Our observation highlights the importance of long-term doxycycline use for MD full remission and underlines the importance of regimens with better safety profiles such as the one reported in this case
Chen 1997 [59]	1. Male 44 years Rosacea 2. Male 63 years Rosacea 3. Female 63 years Rosacea	1. Tetracycline 500 mg b.i.d. for 6 weeks, minocycline 100 mg b.i.d., ciprofloxacin 500 mg b.i.d. 2. Tetracycline 500 mg b.i.d. and topical metronidazole b.i.d. 3. Tetracycline 500 mg b.i.d. and topical metronidazole b.i.d.	Not reported	1. Unresponsive to tetracycline, minocycline and ciprofloxacin 2. Edema was unchanged 3. No significant improvement	
Fujimoto 2015 [2]	Male 74 years	(Previous oral betamethasone 1.5 mg/day for 1 week was not effective) Minocycline 50 mg/day for 4 weeks and then increased to 100 mg/day for 4 months	8 months	Gradually improvement, some eyelid edema persisted after minocycline	The authors speculate that long-term use of tetracycline is effective only in Morbihan disease with abundant mast cell infiltration
Kabuto 2015 [50]	Female 64 years	Minocycline 100 mg/day for 6 months (one month combined with fexofenadine but no effect and therefore stopped)	Not reported	Improvement started after 4 months, edema disappeared after 6 months	Speculation: long-term tetracycline is effective in cases with increased mast cell infiltration
Macellaro 2018 [51]	Female 28 years	Doxycycline 100 mg b.i.d. for 30 days	Not reported	Complete response	
Okubo 2017 [52]	1. Male 56 years	1. Minocycline 100 mg/day for 7 months, change to doxycycline 200 mg/day because of side effects for 7 months	1. 10 months disease-free	1. Improvement started after minocycline, marked improvement at the end of treatment	Treatment response was associated with mast cell infiltration

	2. Male 32 years 3. Male 63 years 4. Male 67 years All rosacea	2. Doxycycline 200 mg/day for 12 months 3. Doxycycline 200 mg for 9 months 4. Doxycycline 200 mg/day for 5 months	2. 10 months disease-free 3. 6 months disease-free 4. 8 months disease-free	2. Marked improvement 3. Marked improvement 4. Marked improvement	
Rizzo 2021 [53]	Male 28 years	Minocycline 100 mg/day, topical metronidazole twice/day, for 2 months	Not reported	Significant improvement of erythema and papules, partial improvement of edema	Confocal microscopy can be useful in detecting reduction of Demodex mites density and inflammatory cells
Suzuki 2023 [54]	Male 70 years Rosacea	Tetracycline (dosage unknown)	Not reported	Improvement	Clinical image, little information provided)
Uhara 2000 [55]	Male 53 years Acneiform eruptions perioral region	Fleroxacin 100 mg/day for 2 weeks	6 months	Marked reduction of edema after several days, after 6 months some improvement of erythema and acneiform eruptions	Although facial edema (resistant to minocycline in our patient) immediately improved after administration of fleroxacin, spontaneous remission cannot be excluded
Utikal 2005 [56]	Male 62 years Rosacea	Minocycline 50 mg b.i.d. combined with metronidazole 2% cream for 4 weeks	Not reported	Partial improvement mainly of inflammatory lesions, not of edema	
Vasconcelos 2016 [23]	Male 39 years Rosacea	Tetracycline b.i.d. for 30 days	Not reported	No improvement	
TREATMENT WITH ANTIBIOTICS COMBINED WITH CORTICOSTEROIDS					
Camacho-Martinez 1990 [57]	1. Male 18 years 2. Male 17 years Both with acne	1. Antibiotics (?) followed by prednisone 20 mg/day, duration unknown. Repeated courses 2. Antibiotics (?) followed by prednisone 15 mg/day, duration unknown. Repeated courses	1. Not reported 2. Not reported	1. Induration disappeared but recurrence after discontinuation each time 2. Solid edema disappeared but recurrence after discontinuation	
Lai 2004 [58]	Male 51 years Rosacea	Minocycline (dosage unknown) and later prednisone 50 mg/ day for 1 month	6 months	Minocycline had good effect on rosacea, not on lymphoedema. Prednisone had no effect either on lymphoedema	

Mahajan 1998 [59]	Male 18 years Acne	Minocycline 100 mg/day, topical erythromycin 2% cream, benzoyl peroxide 2.5% gel and prednisolone 30 mg/day tapered by 5 mg every 10 days	Not reported	Good response of acne lesions to oral and topical antibiotics Definite reduction of edema of forehead, nose periorbital areas, moderate improvement glabellar area, after systemic corticosteroids	
Morales-Burgos 2009 [60]	Female 58 years Rosacea	Doxycycline 100-200 mg/ day for 3.5 months followed by prednisone 60 mg tapered over a period of 2 weeks	Not reported	Prednisone had initially good effect but immediate recurrence after stopping prednisone	Doxycycline seemed to have no effect after which prednisone was started
Nagasaka 2008 [6]	Male 70 years Rosacea	Minocycline 100 mg b.i.d. and oral tranilast 100 mg 3 times a day for 2 months followed by prednisolone 10 mg b.i.d. for unknown time	A few months	Prednisone resulted in marked improvement but recurrence after stopping within few months	
Ranu 2012 [61]	Male 45 years Rosacea	Doxycycline 100 mg b.i.d. for 6 weeks followed by prednisolone 20 mg/day for 2 weeks and 10 mg/day for 1 week because of blurring of vision. Doxycycline was continued, for 12 weeks in total	Not reported	Marginal improvement of the erythema, the edema persisted after 6 weeks doxycycline. After combining with prednisolone, edema and erythema subsided remarkably resulting in complete response. No recurrence	
Scerri 1996 [62]	Male 71 years Rosacea	Metronidazole 400 mg/day, for 4 months combined with reducing courses prednisone starting at 30 mg/day, followed by metronidazole 200 mg/day	Not reported	Marked reduction of facial swelling and some improvement of erythema	
SURGICAL DEBULKING					
Belousova 2020 [14]	Female 56 years Rosacea	Surgical excision of edematous upper eyelid	Not reported	Not reported	
Bernardini 2000 [63]	1. Female 53 years 2. Female 68 years Both with rosacea	Surgical debulking	Not reported	Very satisfactory cosmetic and functional improvement	Typically eyelid lymphedema in these two patients

Chalasanani 2010 [64]	1. Male 39 years 2. Male 57 years 3. Male 78 years 4. Male 66 years 5. Female 38 years 6. Male 71 years 7. Male 73 years 8. Male 56 years 9. Male 75 years All rosacea	1. Observation 2. Surgical resection 3. Observation 4. Doxycycline 5. Doxycycline 6. Surgical resection 7. Surgical resection 8. Surgical resection 9. Surgical resection	1. Seen once 2. 10 months 3. Seen once 4. Seen once 5. 52 months 6. 39 months 7. 10 months 8. 38 months 9. 2 months	1. Not applicable 2. Improvement 3. Not applicable 4. No improvement 5. Improvement 6. Improvement 7. Improvement 8. Improvement 9. Improvement	Surgical debulking is effective for chronic eyelid lymphedema
Hattori 2021 [65]	Male 32 years	Lymphaticovenous anastomosis surgery and blepharoplasty	1 year	Significant improvement of visual field	
Marzano 2004 [66]	Male 66 years Rosacea	Upper eyelid blepharoplasty	A few months	Acceptable result after blepharoplasty, bilateral swelling recurred over a few months	Blepharochalasis was considered as diagnosis, but patient did not have all the characteristics of floppy eyelid syndrome
Méndez-Fernández 1997 [67]	Male 65 years Acne as child	Surgical debulking and skin grafting, multiple revisions including blepharoplasties and lid-lightening procedures	Not reported	Successful, but several postoperative complications. Multiple revisions were required because of further lymphedema and ectropion	Surgery is probably the last link in referral chain for this difficult to treat condition
O'Donnell 1992 [68]	Male 80 years Rosacea	Surgical debulking	Not reported	Good function of eyelid and restoration of vision	
VARIOUS COMBINATION TREATMENTS					
Aboutaam 2018 [69]	Male 51 years Rosacea	Isotretinoin 0.5 mg/kg/day and furosemide 40 mg/day for 3 months	Not reported	Slight improvement	
Aksoy 2012 [70]	Female 53 years	(Previous treatments loratadine, levocetirizine en fexofenadine without success) Indapamide 2.5mg/day, metronidazole cream 1% and oral metronidazole 500 mg b.i.d. for 3 months	At least a year	Erythematous edema attacks completely stopped and facial erythematous edema decreased significantly. After recurrence treatment was restarted for a year with success, then stopped and continued with azelaic acid	
Barragán Estudillo 2012 [71]	Male 21 years	Isotretinoin 40 mg/day and sulfone 100 mg/day	One month	Good response	

Bechara 2004 [72]	Male 67 years	CO ₂ laser blepharoplasty	6 months	Good cosmetic results, marked improvement of visual impairment, no recurrence	CO ₂ incisions tend to bleed less than traditional incision by scalpels and scissors. Possible occlusion of lymphatic vessels by laser beam, resulting in a decreased relapse rate of facial edema compared to conventional blepharoplasty
Boparai 2019 [1]	1. Female 40 years 2. Male 61 years Both rosacea	1. Topical metronidazole and sulfur wash for 1.5 year 2. Isotretinoin 20 mg b.i.d. with 4-week tapered prednisone	1. 1.5 years 2. Lost to follow-up	1. Minimal improvement 2. Not reported	
Borman 2021 [73]	Male 35 years	Manual lymphatic drainage (MLD) 15 sessions Kinesio taping 2/week followed by nighttime pressure face mask Self-MLD and self-exercise	2 months	Reduction of signs and symptoms at follow-up evaluation 2 months later	
Bundino 1991 [74]	Male 62 years Rosacea	Tetracycline, metronidazole, antituberculosis drugs, systemic corticosteroids and thalidomide	5 years	No improvement	
Carruth 2017 [75]	1. Male 54 years 2. Male 74 years 3. Male 64 years 4. Male 62 years 5. Female 57 years All rosacea	1. Doxycycline and prednisone, 5 years later followed by surgical debulking with repeated intralesional corticosteroids 2. Doxycycline followed by surgical debulking 3. Surgical debulking 4. Repeated intralesional corticosteroids 5. Intralesional corticosteroids	1. 6 months 2. Not reported 3. 6 months 4. Not reported 5. 3 months	1. Recurrent complaints with improvement after treatment 2. Partial response 3. Improved with residual edema and erythema 4. Recurrent complaints with successful reduction after treatment 5. Improvement	Variable responses to surgery, but combinations with intralesional corticosteroids seem to lead to more beneficial outcome
Çinar 2021 [76]	Male 18 years Acne	Complete decongestive therapy (CDT) including manual lymphatic drainage (MLD), 24 sessions total 8	Not reported	Improvement of volume of the facial area, improvement of participant's reported	

		weeks, compression therapy, remedial exercises, skin care and patient education		outcomes including lymphedema-feeling, body-image perception, anxiety	
Connelly 1985 [8]	3 male, 1 female Mean age 20 years All acne	1. Topical acne preparations, hot water injections in indurated area, typhoid fever therapy, x-ray treatments, duration unknown 2. Erythromycin stearate for acne, for 15 months, elastic facial stocking 3. Continuing tetracycline hydrochloride for acne, elastic facial stocking 4. Oral corticosteroids for 6 weeks, antihistamine for 1 week, topical and oral antibiotics for acne	1. Not reported 2. Not reported 3. 2 months, 6 months 4. Not reported	1. Improved condition, edema decreased noticeably 2. Edema unchanged 3. Edema unchanged 4. Edema unchanged	4 patients with acne vulgaris, and development of persistent facial edema
Donthi 2021 [18]	1. Male 67 years Rosacea 2. Male 50 years Rosacea and acne vulgaris	1. Hydrocortisone 2.5% cream, brimonidine 0.33% gel, metronidazole gel and doxycycline 100 mg b.i.d. for 3 months 2. Permethrin later replaced by brimonidine 0.33% gel, hydrocortisone 2.5% cream and doxycycline 100 mg b.i.d. for 6 months	1. 1 year 2. 1 year	1. Disease resolution 2. Complete resolution	
Dwyer 1992 [77]	Male 20 years Acne	Oxytetracycline for 4 months followed by prednisolone for 1 week, followed by isotretinoin (stopped within 4 weeks because of intolerance), antihistamines and an oral diuretic	11 months	Resolution of acne but edema persisted with no effect of oxytetracycline, prednisolone, isotretinoin, antihistamines, oral diuretic. 4 months after last treatment (6 months after resolution of acne) facial oedema began to improve and this resulted in marked improvement 7 months later	The results after treatment suggests that the prognosis in acne-associated oedema may be better than has been reported and may not always depend on specific treatment with isotretinoin or steroids.

				(13 months after resolution of the acne)	
Erbađci 2000 [78]	Male 35 years Rosacea	Isotretinoin 0.7 mg/day for 12 months followed by prednisolone 30 mg/day, metronidazole 500 mg/day and ketotifen 2 mg/day for 6 weeks then tapering	Not reported	No effect of isotretinoin but considerable improvement of lymphoedema with prednisolone, oral metronidazole and ketotifen. Complete resolution of erythema and inflammatory lesions	
Franco 2008 [79]	Male 65 years Rosacea	Antihistamines and lymph drainage	Not reported	Improvement	Few details are provided
Helander 1987 [80]	1. Female 20 years Acne	1. (Previous treatment with prednisone 30 mg, tetracycline, chloroquine phosphate). Clofazimine 100 mg 4 times combined with isotretinoin 30 mg/day for 6-7 months followed by lymph massage 1/week for 15 weeks	1. 8 months after lymph massage	1. No effect/recurrence after prednisone 30 mg, tetracycline, chloroquine phosphate. After 20 weeks isotretinoin 30 mg/day and 17 weeks clofazimine swelling eyelids disappeared, and swelling diminished 50% forehead, nasal bridge and cheeks, 2 months later 75% reduction edema of forehead and cheeks, 8 months after lymph massage condition unchanged	
	2. Male 18 years Acne	2. Isotretinoin 50 mg/day for 12 weeks, followed by 40 mg/day for the next 12 weeks, followed by lymph massage 1/week for 15 weeks	2. Not reported	2. After 12 weeks isotretinoin marked reduction of acne lesions, edema of the eye lids disappeared, 25% reduction of edema forehead, nasal bridge and cheeks, after 24 weeks isotretinoin 50% reduction in edema	

Hernández-Cano 1999 [81]	Female 23 years Acne	(Previous treatments with topical and systemic antibiotics no effect) Prednisone 1 mg/kg per day for 1 month and lymph massage	3 years	Complete response	
Hölzle 1995 [82]	Male 62 years	Topical steroids, tannin- and sulfur preparations, metronidazole, erythromycin, tetracycline, antihistamines, isotretinoin, manual lymph drainage	Not reported	No improvement during 7 years of treatment	
Jay 2022 [83]	Female 72 years Rosacea	Osteopathic manipulative treatment (OMT), weekly for 1 month	1 month	Decreased swelling after the first OMT session, improvement continued over the next month	Treatment of somatic dysfunction utilizing OMT techniques can augment treatment of rosacea-associated, facial lymphedema
Kafi 2019 [84]	Female 56 years	Lymecycline 300 mg b.i.d. for 3 months, later isotretinoin 10–20 mg/day for 4 months. Omalizumab injections monthly, for 5 months with an initial dose of 450 mg and consecutive doses of 300 mg, maintenance treatment every 4–6 weeks was given for a further 2 months	6 months	No effect after lymecycline or isotretinoin. Complete clearance after 5 months of monthly omalizumab No relapse at follow up. The quality of life was markedly improved after omalizumab injections	
Kilinc 2003 [9]	Male 25 years Acne	After tetracycline 500 mg b.i.d. for 2 months isotretinoin 40 mg/day (0.5 mg/kg), stopped after 4 months because of side effects. Followed by colchicum 1.5 mg/day without effect, intralesional triamcinolone 5 mg/ml injections monthly, for 5 months	2-3 weeks	No effect after tetracycline. Temporary improvement, better quality of life after triamcinolone injections	Suggestion: anti-inflammatory drugs, such as isotretinoin or corticosteroids are only recommended in the earlier stages of swelling
Kim 2019 [85]	1. Female 67 years 2. Male 73 years 3. Female 42 years 4. Male 54 years 5. Female 59 years	Surgical eyelid reduction followed by lymphatic drainage was performed for all 6 patients. 3. Doxycycline 200 mg/day because of intermittent swelling	6 months	All showed marked improvement 1,2 no recurrence 3. Patient felt that surgery had afforded significant improvement, but developed	The histological features were of two different types: I. severe inflammatory cell infiltration, including mast cells (patient 4, 5, 6) and II. severe dermal oedema, interface dermatitis and sun

	6. Male 61 years			slow intermittent swelling, less than previously. Doxycycline resulted in gradually relieve of symptoms 4,5,6 Recurrence	damage (patient 1, 2). Patient 3 exhibited mixed histological features with moderate dermal oedema and moderate to-severe inflammatory lymphohistiocytic infiltration with abundant mast cells. Interestingly, the three patients who experienced recurrences (patient 4, 5, 6) were of the histological type I, and the two patients who did not experience recurrence were of histological type II. Patient 3 who developed intermittent eyelid swelling after surgery had mixed histological features
Kou 2014 [86]	Male 30 years Extra facial lupus miliaris disseminatus faciei (LMDF)	Roxithromycin 300 mg/day for 1 year Surgical debulking	Not reported	Roxithromycin resulted only in minimal improvement of edema. Significant improvement after surgical treatment	
Kuhn-Régier 2017 [11]	1. Male 18 years Acne 2. Male 20 years Acne	1. Isotretinoin 20 mg/day for 2 months combined with 2 mg/kg prednisone 2. Isotretinoin 20 mg/day for 8 months and an antihistamine (?)	1. Not reported 2. Not reported	1. Complete regression 2. Facial edema slowly cleared	
Kuraitis 2020 [13]	Female 32 years Rosacea	(Previous: topical corticosteroids, topical antibiotics, several systemic therapies, isotretinoin 40 mg/day for 4 months, methotrexate 15 mg/week for 8 months, all without improvement Oral ivermectin 21 mg every 2-4 weeks and intralesional Kenalog 5 mg/ml injections every 6-8 weeks		Rapid improvement of erythema, pustules as well as in swelling and induration of upper eyelids after ivermectin and intralesional corticosteroid injections	

Kutlay 2019 [87]	1. Female 51 years 2. Female 45 years Rosacea	1.(Previous tetracycline, doxycycline 100 mg for 7 months and repeated methylprednisolone injections were unsuccessful) Complete decongestive therapy (CDT) 10-15 sessions. 2. (Previous treatment doxycycline 100 mg and topical clobetasone butyrate for unknown time was unsuccessful) 15 CDT session	Not reported for both patients	1. Almost completely resolved 2. Moderate response	CDT (modified for use in head and neck lymphedema) consists of manual lymphatic drainage, compression therapy, skin care, exercise, and self-care
Kwok 2015 [88]	Male 17 years	Isotretinoin for 1 year was successful but after recurrence side effects of isotretinoin. Doxycycline combined with oral corticosteroids (dose unknown) followed by maintenance with doxycycline	Not reported	Isotretinoin was successful but recurrence and side effects He responded as well to doxycycline with oral corticosteroids	
Lamparter 2010 [89]	Female 53 years	Doxycycline 100 mg/day for 5 weeks followed by metronidazole 250 mg b.i.d., then isotretinoin 20 mg and then ketotifen 1 mg b.i.d. for 4 weeks. Eye lid reduction surgery followed by lymphatic drainage twice /week, oxytetracycline eye ointment	6 months	No improvement for/after oral treatments, significant functional and cosmetic improvement after surgery	
Laugier 1981 [90]	1. Male 59 years 2. Female 66 years 3. Female 62 years 4. Male 59 years 5. Female 64 years	Thalidomide 100 mg/day	Not reported	1. No effect 2. Almost complete response 3. Partial response 4. No effect 5. Good response	
Leigheb 1993 [91]	Male 61 years	Blepharoplasty, rifampicin, betamethasone, deflazacort	9 years	Partial improvement but then relapses	
Messikh 2012 [92]	1. Male 38 years	1. (Previous treatments with ketoconazole, methylprednisolone, chloroquine, thalidomide combined	1. 16 years	1. Complete response Patient satisfied with result	According to the authors of this case series diuretics may be of

	<p>2. Male 66 years</p> <p>3. Male 76 years</p>	<p>with prednisone, clofazimine, metronidazole and isotretinoin without success) Furosemide 60 mg/day for 6 weeks</p> <p>2. (Previous treatments with doxycycline, crotamiton, hydroxychloroquine) Furosemide 60 mg/day for 6 weeks</p> <p>3. (Previous treatments with hydroxychloroquine, oral corticosteroids, blepharoplasty, isotretinoin) Furosemide 60 mg/day and spironolactone 75 mg b.i.d.</p>	<p>2. 4 years</p> <p>3. 1 year</p>	<p>2. Almost complete response</p> <p>3. Partial response with corticosteroids and blepharoplasty. Almost complete response after diuretics</p>	<p>value since they help significantly reduce swelling</p>
Patel 2008 [93]	<p>Male 24 years</p> <p>Acne</p>	<p>Topical steroids, several oral antibiotics without improvement. Isotretinoin 1 mg/kg/day for 3 months, then prednisone 30mg/day for 1 month was added</p>	<p>Not reported</p>	<p>After 3 months minimal improvement of edema, after 4 months (prednisone was added) no improvement Patient discontinued therapy</p>	
Pflibsen 2020 [94]	<p>Male 55 years</p> <p>Rosacea</p>	<p>(Previous: doxycycline 100mg b.i.d. and topical metronidazole 1% gel for 6 months with no significant effect) Surgical debulking with blepharoplasty. Methotrexate and adalimumab for symptoms of the upper and middle thirds of the face with no effect. Then prednisone was initiated but discontinued because of uncontrolled diabetes Additional surgical debulking and injections of triamcinolone (40 mg/ml) 1 ml, because of recurrent bilateral upper and lower eyelid edema 1 year later</p>	<p>Lost to follow up</p>	<p>Significant improvement of surgical debulking Methotrexate and adalimumab had no effect on edema</p> <p>Symptoms improved after additional surgical debulking and addition of steroid injections</p>	

		Two years later again recurrence and isotretinoin for 1 year with no effect		Isotretinoin had no effect on edema	
Plange 2006 [95]	Female 44 years	Prednisolone 0.5 mg/kg per day for 4 weeks	Not reported	Improvement	Therapy was stopped because of weight gain
Ramirez 2019 [7]	1. Male 85 years Rosacea 2. Female 64 years Rosacea 3. Male 67 years 4. Male 67 years 5. Female 41 years 6. Female 43 years 7. Male 59 years 8. Female 43 years 9. Male 56 years 10. Male 60 years 11. Male 58 years 12. Male 62 years 13. Male 54 years 14. Male 64 years	1. Tacrolimus 2. Azelaic acid 3. Surgical reduction 4. Surgical reduction 5. Minocycline and tacrolimus 6. Surgical reduction 7. Surgical reduction 8. Surgical reduction 9. Surgical reduction 10. Isotretinoin 11. Surgical reduction 12. Prednisolone 13. Doxycycline 14. Surgical reduction	1. 48 months 2. 24 months 3. 24 months 4. 60 months 5. 5 months 6. 84 months 7. 60 months 8. 30 months 9. 25 months 10. 10 months 11. 45 months 12. 43 months 13. 20 months 14. 50 months	1. Stable 2. Recurrence 3. Recurrence at 24 months, new surgery 4. Recurrence at 5 years, new surgery 5. Stable 6. Resolution 7. Recurrence 8. Recurrence 9. Stable 10. Recurrence 11. Recurrence 12. Recurrence 13. Stable 14. Recurrence	Most constant histopathologic features in these series included dilated vessels in the dermis and presence of mast cells.
Renieri 2011 [96]	1. Female 53 years 2. Male 53 years 3. Male 53 years	1. Eyelid blepharoplasty, followed by lymph drainage and oxytetracycline eye ointment 2. Intralesional triamcinolone injections, total 40 mg upper- and lower lid each eye, tapered 30 mg triamcinolone injections/3 months, lymph drainage 3. Intralesional triamcinolone injections, lymph drainage	1. 13 months 2. Not reported 3. > 9 months?	1. Improvement 2. Improvement, 11 months after start injections 3. Improvement, 9 months after first injection recurrence for which injections were repeated	1. and 2. Previous treatment with combination Isotretinoin and ketotifen was ineffective. 2. Interesting finding: intralesional triamcinolone was effective where systemic steroids failed 2. and 3. Lymph drainage contributes?/ resulted in lasting effect 1. and 5. Blepharoplasty in combination with intralesional triamcinolone injections resulted

	4. Male 60 years 5. Male 49 years All rosacea	4. Topical metronidazole and permethrin 5. Blepharoplasty, intralesional triamcinolone injections	4. 14 months 5. 1 month	4. No response 5. Good result	in (good) improvement after ineffective systemic treatment
Torres-Gomez 2018 [97]	Male 45 years	Corticosteroids, ciclosporin and isotretinoin	Not reported	No improvement	
Tosti 1987 [98]	2 Male identical twins 14 years Acne	Betamethasone 1.5 mg/day stopped after 2 weeks because of lack of improvement. Topical and oral antibiotics for the acne	Not reported	No response	
Tsiogka 2017 [99]	Male 44 years	(Previous long-term antibiotics with no improvement) Bilateral eyelid debulking twice with 2 years interval Long-term therapy with intralesional triamcinolone injections every 4 weeks for 14 months	8 months after discontinuing injections on left side	Only transient improvement after eyelid debulking. Subjective and objective improvement of edema within 4 months. Hence, treatment was maintained and further improvement was observed. No recurrence of left side at follow up, injections on right side were still continued	
Weeraman 2019 [100]	Male 46 years	Doxycycline 40 mg/day modified release and 1% pimecrolimus cream for 3 months Debulking surgery on the right infra-orbital cheek, followed by an intralesional injection of 40 mg triamcinolone together with doxycycline 100mg/day with 0.1% tacrolimus ointment for 3 months because of mild upper facial erythema and pustules.		No improvement of swelling after doxycycline Improvement of the swelling 1 month after surgery and intralesional triamcinolone, 6 months later the swelling of the right infra-orbital cheek reappeared, Patient had not noticed much improvement after isotretinoin and brimonidine gel	

		6 Months after surgery, isotretinoin 20 mg/day for 1.5 years and subsequently 10 mg/day with brimonidine gel was initiated because of reappearance of swelling. Isotretinoin was stopped after more than 2 years to receive laser treatment for erythema and telangiectasia. Ketotifen 1 mg/day was commenced more than 0.5 year later and discontinued after 1 month because of side effects. Manual lymphatic drainage together with compression mask		Little improvement following ketotifen Patient has not noticed improvement after manual lymphatic drainage and compression mask	
Yu 2018 [101]	Male 42 years	Tripterygium wilfordii (DND-PHARMA; Zhejiang DND Pharmaceutical, Xinchang, Zhejiang, China) 60 mg/day	Not reported	Significant improvement in 6 weeks	The adverse effects of T. wilfordii include gastrointestinal discomfort, menstrual disorders, reproduction toxicity, mild myelosuppression and liver function impairment. These side effects are reversible
Yvon 2020 [5] Only 2 had former diagnosis of rosacea All had mild rosacea type skin	Males 8, Females 2 Mean 67 years Patient 1 72 years Patient 2 52 years	1. Tacrolimus 0.03% b.i.d. for 2 months, followed by prednisone 40 mg for one month followed by isotretinoin 30 mg, increased to 60 mg after 1 month, triamcinolone 1 mg intralesional injections, bilateral festoon excision 2. Intravenous methylprednisolone (weekly pulses) for 6 weeks, followed by isotretinoin 30 mg/day	1. Not reported 2. Not reported	1. Poor response to tacrolimus and prednisone, partial response to isotretinoin, good response but recurrence after intralesional triamcinolone, good response to surgical treatment 2. Poor response to methylprednisolone and isotretinoin	In these case series over half of the patients received a tetracycline-based antibiotic for 3 months or more, but without marked improvement. Good results were achieved with isotretinoin, intralesional injection of triamcinolone, and/or debulking surgery, but recurrences occur frequently even after a long period of stability.

	Patient 3 75 years	then reduced to 10 mg/day after 1.5 month 3. Doxycycline 100 mg /day for 3 months poor response, then bilateral debulking and minor midface lift	3. Not reported	3. Poor response after doxycycline, good response after surgical treatment	
	Patient 4 48 years	4. Doxycycline 100 mg/day for 6 months, isotretinoin, triamcinolone 1 mg injection for right lower lid	4. Not reported	4. Poor response for doxycycline, good response for first triamcinolone injection, partial response for second injection because of relapse	
	Patient 5 71 years	5. Metronidazole, poor response. More recently topical ivermectin, doxycycline, isotretinoin, some skin excision, subsequent direct brow lift	5. Not reported	5. Poor response for metronidazole, isotretinoin better response than surgery	
	Patient 6 78 years	6. Doxycycline 500 mg b.i.d. for 12 months, skin excision and split-skin grafting	6. Not reported	6. No response for doxycycline, Improvement in lower visual field, but subsequent cicatricial ectropion.	
	Patient 7 75 years	7. Isotretinoin 10 mg/day for 3 months, lymecycline 408 mg/day for 4 months, intralesional dexamethasone 2x, blepharoplasty and debulking	7. Not reported	7. No change with isotretinoin or lymecycline, no difference with intralesional dexamethasone, progression after blepharoplasty and debulking	
	Patient 8 88 years	8. Multiple previous treatments: doxycycline, minocycline, lymecycline, isotretinoin. Blepharoplasty and debulking	8. Not reported	8. Good response after blepharoplasty and debulking	
	Patient 9 51 years	9. Blepharoplasty	9. Not reported	9. Improved	
	Patient 10 62 years	10. Blepharoplasty	10. Not reported	10. Improvement in visual field	

Zhang 2021 [102]	Female 59 years	Blepharoplasty followed by intralesional injections of triamcinolone (80 mg), isotretinoin (20 mg/day) and tetracyclines (500 mg/day) for 3 months.	1 year	Improvement of vision field and sluggish progression of facial mass during follow up	
Zhou 2022 [103]	Female 55 years Rosacea	(Prednisone acetate and tripterigyum wilfordii for 4 months, stopped because of adverse reactions) Total glucosides of paeony capsules 0.9 g 3 times a day for 4 months	1 year	Significant reduction of edema after 1 month, Complete disappearance of facial edema after 4 months. No recurrence at follow up	Total glucosides of paeony capsules is a Chinese patent medicine, extracted from <i>Radix paeoniae alba</i> with therapeutic properties such as anti-inflammatory and immune regulation effects
