**Supplementary table 1.** Studies included in the network meta-analysis on various treatments for melasma

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Year /Author | Treatment | *N* | Age | Skin type | Duration (weeks) | Change of MASI (mean ± SD) | Adverse effects |
| 2020 Minni K[53] | oTA + FbTc | 65 | 36 | III1, IV15, Ⅴ48, Ⅵ1 | 12 | 8.19 ± 3.90 | Erythema 11, burning 9, gastrointestinal complaints |
| FbTc | 65 | 38.5 | IV18, Ⅴ47 | 5.07 ± 3.47 | Erythema 17, burning 16 |
| **2020 Kaur A[54]** | **MN + tTA** | **40** | **33.15** | **IV36, Ⅴ4** | **8** | **2.84 ± 1.55** | **Erythema 7, pruritus 5, burning 1, hyperpigmentation 2, dryness 22** |
| **MN** | **0.80 ± 1.82** | **Erythema 9, pruritus 4, burning 2, hyperpigmentation 2, dryness 22** |
| 2020 Cassiano D[55] | Placebo | 16 | ＞18 |  | 8 | 0.40 ± 4.10 | TA: nausea, abdominal pain, hair loss, blurred vision, headache 1; MN: herpes simplex 3 |
| oTA | 16 |  | 3.20 ± 4.63 |
| MN | 16 |  | 3.00 ± 3.67 |
| oTA + MN | 16 |  | 2.80 ± 7.18 |
| 2020 Shihab N[56] | oTA + HQ | 25 | 46.6 ± 5.5 |  | 12 | 4.93 ± 2.14 | HQ: erythema, pruritus 3; TA: changes in the menstrual cycle 1 |
| HQ | 25 | 46.4 ± 5.8 |  | 0.89 ± 2.01 |
| **2020 Kaleem S[57]** | **tTA** | **60** | **36 ± 7.9** | **III34, IV24, Ⅴ2** | **12** | **1.67 ± 2.22** | **Erythema 6, swelling 31, burning 8, irritation 15** |
| **Placebo** | **0.01 ± 2.65** |  |
| **2020 Otb S[58]** | tTA | 27 | 44 ± 6.3 | Ⅱ2, Ⅲ18, IV7 | 24 | 1.89 ± 2.15 | No |
| AFL-Er:YAG | 0.95 ± 2.44 | No |
| 2020, Shamsi MS[59] | tTA | 30 | 26.1 ± 0.6 | Ⅱ1, Ⅲ8, IV12, Ⅴ9 | 12 | 6.05 ± 4.79 | Erythema 25, PIH 2 |
| HQ | 30 | Ⅱ2, III6, IV14, Ⅴ8 | 6.40 ± 4.65 | Erythema 7, PIH 4 |
| **2020 Mekawy KMM[60]** | **MN** | **30** | **41.9 ± 7.8** | **Ⅱ5, Ⅲ23, IV2** | **14** | **1.84 ± 1.69** | **PIH 3** |
| **AFL-CO2** | **1.73 ± 1.69** |  |
| 2019 Garg S[61] | IPL | 20 | 22–46 | III33, IV27 | 24 | 4.59 ± 5.20 | Dryness |
| QSND | 20 | 4.68 ± 4.55 | PIH 3, acne breakouts 2 |
| AFL-Er:YAG | 20 | 7.58 ± 8.12 | PIH 2, herpes labialis 1 |
| 2019 Wang YJ[39] | PICO (3 sessions) | 9 | 40.4 |  | 20 | 4.20 ± 4.43 | Erythema 2, focal desquamation 1 |
| PICO (5 sessions) | 11 | 46.4 |  | 4.00 ± 3.93 | Erythema 3, PIH 2, focal desquamation 1 |
| TCC | 6 | 50 |  | 5.90 ± 4.49 | Dryness, erythema, and itching 2 |
| **2019 Saka S[62]** | **tTA** | **38** | **40.16 ± 5.76** | **Epidermal 24; dermal 5; mixed 9** | **12** | **1.11 ± 1.66** | **Erythema and burning** |
| **Placebo** | **0.19 ± 1.65** |  |
| 2019 Janney MS[63] | tTA | 50 | 35.86 ± 7.51 | Ⅲ2, Ⅳ26, Ⅴ22 | 12 | 2.92 ± 3.10 |  |
| HQ | 50 | 36.32 ± 7.65 | Ⅲ2, Ⅳ24, Ⅴ24 | 2.39 ± 3.51 |  |
| **2019 Zhao H[64]** | **tTA** | **17** | **39.47 ± 6.05** | **III13, IV4** | **8** | **4.06 ± 3.38** | **Erythema 2, stuffy 1** |
| **tVC** | **3.62 ± 3.88** |
| **2018 Tehranchinia Z[65]** | **tTA + HQ** | **55** | **35.93 ± 5.9** | **Ⅱ9, Ⅲ35, Ⅳ11** | **16** | **3.39 ± 1.62** | **Erythema 26, pruritus 6** |
| **HQ** | **2.27 ± 1.69** | **Erythema 28, pruritus 7** |
| **2018 Chalermchai T[66]** | **PICO + HQ** | **30** | **47.5 ± 6.8** | **Ⅲ5, IV25** | **12** | **5.94 ± 2.95** | **Erythema 2, skin desquamation 2, burning 1** |
| **HQ** | **5.30 ± 2.95** |  |
| 2018 Colferai MMT[67] | oTA | 20 | 45.75 |  | 12 | 10.10 ± 7.88 | Gastrointestinal tract 7 |
| Placebo | 17 | 42.88 |  | 1.70 ± 6.89 | No |
| **2018 Badawi AM[31]** | **AFL-Er:YAG + HQ** | **30** | **37.87 ± 7.97** | **Ⅲ11, IV12, V7** | **10** | **5.57 ± 2.85** | **Erythema, burning, itching** |
| **HQ** | **2.28 ± 2.84** | **Erythema 5, burning, itching** |
| 2018 Vanaman Wilson MJ[68] | Diode laser + HQ | 20 | 46 ± 10.9 | Ⅲ14, Ⅳ4, Ⅴ2 | 12 | 7.40 ± 6.46 |  |
| Diode laser + placebo | 20 | 47.2 ± 8.5 | Ⅲ8, Ⅳ10, Ⅴ4 | 9.70 ± 9.22 |  |
| 2018 Tawfic SO[69] | AFL-CO2 | 28 | 39.61 ± 6.71 | Ⅲ14, IV–Ⅴ14 | 18-26 | 1.75 ± 4.38 | Burning 28 |
| AFL-CO2+tTA | 13 | 40.45 ± 8.23 | Ⅲ6, IV–Ⅴ7 | 1.69 ± 4.12 | Burning 13, PIH 2 |
| AFL-CO2+tTA | 15 | 38.80 ± 5.21 | Ⅲ8, IV–Ⅴ7 | 1.45 ± 4.53 | Burning 15 |
| 2017 Atefi N[70] | tTA | 30 | 38.10 ± 6.27 |  | 12 | 2.47 ± 0.93 |  |
| HQ | 30 | 39.97 ± 7.86 |  | 2.07 ± 0.82 |  |
| **2017 Choi YJ[71]** | **PICO + HQ** | **39** | **48.38 ± 6.65** | **Ⅲ22, IV17** | **14** | **3.70 ± 8.90** | **Dermatitis 2** |
| **HQ** | **1.30 ± 9.34** |  |
| 2017 Dayal S[72] | GA peel + AA | 30 | 33.40 ± 7.44 | IV16, V14 | 24 | 9.33 ± 4.07 | Erythema 4, PIH 4, pruritus 2, scaling 2, burning 5 |
| AA | 30 | 33.77 ± 6.11 | IV16, V14 | 6.56 ± 4.30 | Erythema 1, PIH 2, pruritus 5, scaling 1, burning 3 |
| 2017 Lu J[73] | oTA | 41 | 43 | Ⅲ or IV | 8 | 5.26 ± 3.16 | No |
| Placebo | 41 | -0.73 ± 3.16 | No |
| **2017 Abdel-Meguid AM[74]** | **Jessner peel + TCA peel** | **24** | **34.50 ± 7.76** | **Epidermal 14; mixed 10** | **12** | **6.23 ± 4.97** | **Erythema 24, discomfort 15, burning 14, itching 3, crustation 24, PIH 2** |
| **TCA peel** |  | **4.54 ± 5.18** | **Erythema 24, discomfort 3, burning 4, itching 2, crustation 24** |
| 2017 Balevi A[75] | tVC + SA peel | 23 | 36.32 ± 10.19 |  | 8 | 11.36 ± 10.48 |  |
| SA peel | 21 |  | 1.84 ± 10.68 |  |
| **2017 Ustuner P[76]** | **QSND + tVC** | **48** | **37.69 ± 8.24** | **Ⅱ30, Ⅲ18** | **16** | **4.55 ± 3.94** | **Irritation 3, hyperpigmentation 3, hyperpigmentation + hypopigmentation 3** |
| **QSND** | **1.61 ± 4.39** | **Hyperpigmentation 6** |
| **2016 Chung JY[77]** | **IPL + tTA** | **15** | **41.38 ± 4.37** |  | **24** | **5.39 ± 5.08** | **No** |
| **IPL** | **1.47 ± 6.49** | **No** |
| 2016 Lajevardi V[78] | oTA + HQ | 45 | 35.4 ± 5.7 |  | 24 | 7.4 ± 5.8 | Abdominal pain 3, flank pain and edema 1, nausea-vomiting-headache 1 |
| HQ | 43 | 37.3 ± 5.8 |  | 3.5 ± 3.9 |  |
| **2015 Vachiramon V[79]** | **QSND + GA peel** | **15** | **45 (28–69)** | **Ⅲ4, IV9, V2** | **8** | **7.08 ± 2.08** | **Burning 7, erythema 5, hyperpigmentation 2, hypopigmentation 1** |
| QSND | -0.67 ± 2.01 | Burning 5, erythema 3, hyperpigmentation 2, hypopigmentation 1 |
| 2015 Ibrahim ZA[80] | HQ | 20 |  |  | 12 | 6.67 ± 5.05 | Pruritus 8, erythema 4 |
| HQ + GA peel | 20 |  |  | 3.97 ± 3.94 | Erythema 6, erosion 4, scaling 2, crustation 8 |
| HQ + HA peel | 20 |  |  | 7.52 ± 3.93 | Pruritus 4 |
| HQ + GA peel + HA peel | 20 |  |  | 9.14 ± 4.81 | Pruritus 2, erythema 6, scaling 4, crustation 2 |
| Placebo | 20 |  |  | 0.00 ± 2.69 |  |
| 2015 Elfar NN[81] | tTA | 20 | 37.0 ± 4.80 | Epidermal 30; dermal 13; mixed 17 | 12 | 1.86 ± 2.21 | Burning pain 20, wheal 20, erythema 5 |
| GA peel | 20 | 36.45 ± 6.28 | 4.06 ± 3.10 | PIH 6 |
| **2015 Banihashemi M[82]** | **tTA** | **30** | **25–47** |  | **16** | **7.94 ± 2.62** |  |
| **HQ** |  | **7.00 ± 2.25** | **Skin irritation 3** |
| 2015 Padhi T[83] | TCC | 20 |  |  | 8 | 8.43 ± 5.59 | Erythema 3, burning 2 |
| TCC + oTA | 20 |  |  | 16.05 ± 2.99 | Erythema 2, burning 2, PIH 2, oligomenorrhoea 1 |
| 2014 Lee DB[84] | QSND + placebo | 26 | 42.08 ± 6.56 |  | 20 | 2.46 ± 3.55 | Peel:burning 4; QSND: pain and erythema |
| QSND + Jessner peel | 26 | 40.85 ± 7.48 |  | 2.93 ± 3.31 |
| 2014 Yun WJ[85] | QSND + IPL | 12 | 42.6 ± 1.9 |  | 18 | 6.25 ± 4.09 | Burn 1, dry 3 |
| IPL | 12 | 43.4 ± 2.0 |  | 2.83 ± 3.12 |  |
| 2014 Mendoza CG[86] | HQ | 15 | 29.04 ± 7.8 | Epidermal 11; mixed 4 | 8 | 0.55 ± 0.62 |  |
| Placebo | 15 | Epidermal 15 | 0.09 ± 0.12 |  |
| **2014 Truchuelo MT[87]** | **Tretinoin** | **30** | **39** | **Ⅱ18, Ⅲ12** | **12** | **7.00 ± 4.04** |  |
| **Placebo** | **5.20 ± 4.41** |  |
| **2014 Jalaly NY[88]** | **AFL-CO2** | **40** | **42.5 ± 7** | **II21, III16, IV3** | **8** | **6.30 ± 8.91** | **Erythema, burning, edema, scaling** |
| **QSND** | **8.85 ± 8.10** | **Erythema, edema** |
| **2014 Vachiramon V[89]** | **QSND** | **20** | **47.5 ± 6.9** |  | **20** | **8.15 ± 7.62** | **Erythema, stinging** |
| **QSND+IPL** | **2.30 ± 6.81** | **Erythema, stinging, microcrust 14, hypomelanosis 1** |
| 2013 Shin JU[90] | QSND + oTA | 23 | 44.4 ± 7.9 | III or IV | 12 | 2.90 ± 3.55 | Erythema 23, medication-associated heartburn 2, nausea 1 |
| QSND | 21 | 43.2 ± 6.91 | 1.90 ± 3.60 | Erythema 21 |
| **2013 Kim HS[91]** | **QSND** | **26** | **45 (33–64)** | **III or V** | **32** | **2.55 ± 1.36** |  |
| **QSND + NAFL** | **2.58 ± 1.22** | **Erythema, burning, edema, PIH 2** |
| 2013 Deo KS[92] | KA | 20 |  |  | 12 | 5.57 ± 6.70 |  |
| KA + HQ | 20 |  |  | 6.29 ± 4.34 |  |
| KA + betamethasone valerate | 20 |  |  | 3.44 ± 6.99 |  |
| KA + HQ + betamethasone valerate | 20 |  |  | 8.49 ± 8.21 |  |
| 2013 Chaudhary S[93] | Topical regimen + GA | 20 | 34 (21–40) |  | 24 | 12.40 ± 2.94 | Erythema 4, PIH 3, hypertrichosis 1, burning and stinging 9 |
| Topical regimen | 20 |  | 7.27 ± 3.05 |  |
| 2012 Kar HK[94] | Low-fluence QSND | 21 | 34.05 ± 6.79 | IV20, V40 | 12 | 6.49 ± 6.44 | Hypopigmentation 1 |
| GA peel | 19 | 4.35 ± 5.59 | Erythema/Burning 4, PIH 1 |
| High-fluence QSND | 20 | 2.19 ± 4.72 | Erythema/Burning 4, hypopigmentation 5, PIH 6 |
| 2012 Figueiredo SL[95] | IPL | 31 | 43.8 ± 7.2 | Ⅱ3, Ⅲ11, Ⅳ13, Ⅴ4 | 24 | 8.70 ± 6.65 | Erythema, pain, PIH 3 |
| Placebo | 31 | 45.1 ± 4.3 | Ⅱ4, Ⅲ10, Ⅳ13, Ⅴ4 | 0.39 ± 5.28 |  |
| 2012 Bansal C[96] | QSND | 20 | 37.7 ± 6.63 | Ⅲ1, Ⅳ31, Ⅴ28 | 12 | 6.22 ± 4.79 |  |
| AA | 20 | 11.00 ± 6.04 | Burning/Stinging 1 |
| QSND + AA | 20 | 13.79 ± 6.84 | Erythema 1, burning/stinging 1 |
| 2012 Karn D[97] | oTA | 130 | 30.3 ± 9.01 | Epidermal 93; dermal 14; mixed 23 | 12 | 3.24 ± 2.70 | Oligomenorrhea 16, belching 12, abdominal cramps 9 |
| Placebo | 130 | Epidermal 80; dermal 14; mixed 36 | 2.34 ± 3.21 |  |
| **2012 Sobhi RM[98]** | **GA peel** | **14** | **39.36 ± 7.397** | **Ⅳ9, Ⅴ5** | **4** | **1.13 ± 2.68** | **PIH 2, dryness 1, burning 1, blister 4** |
| **tVC** | **1.18 ± 2.85** | **Burning 1, electric shock 1** |
| **2012 Hong SP[99]** | **NAFL** | **17** | **35.4 ± 4.67** | **Ⅲ or Ⅳ** | **12** | **1.75 ± 2.63** | **erythema 3, PIH 5** |
| **TCA peel** | **3.53 ± 2.80** | **erythema 4, PIH 5** |
| 2011 Kroon MW[100] | NAFL | 10 | 35.3 | Ⅱ2, Ⅲ4, Ⅳ3, Ⅴ1 | 12 | -0.19 ± 4.83 | Erythema 75%, burning 58% |
| TCC | 10 | 42 | Ⅱ3, Ⅲ4, Ⅳ2, Ⅴ1 | 1.30 ± 6.81 | Erythema 25%, burning 20%, scaling 55% |
| **2011 Park KY[12]** | **QSND + GA peel** | **16** | **43.94 ± 8.64** | **Ⅲ or Ⅳ** | **5** | **5.80 ± 1.60** | **Erythema, burning, edema** |
| **QSND** | **3.50 ± 1.85** |
| 2011 Farshi S[101] | HQ | 15 | 34.6 ± 6.6 |  | 8 | 1.00 ± 3.41 | Erythema 2, irritation 7, pruritus 1 |
| AA | 14 |  | 3.80 ± 3.20 | Irritation 2 |
| **2011 Faghihi G[102]** | **GA peel** | **63** | **37.3 ± 9.13** |  | **12** | **2.40 ± 3.27** | **PIH 3** |
| **Tretinoin** | **2.70 ± 3.43** | **PIH 1** |
| 2010 Trelles MA[103] | TCC | 10 | 35.6 ± 6.3 | Ⅱ10, Ⅲ12, Ⅳ8 | 4 | 18.10 ± 6.84 |  |
| AFL-CO2 | 10 | 15.30 ± 6.26 | Stinging/Burning |
| AFL-CO2 + TCC | 10 | 20.30 ± 6.71 | Stinging/Burning |
| **2010 Wattanakrai P[104]** | **QSND + HQ** | **22** |  | **Ⅲ10, Ⅳ6, Ⅴ6** | **7** | **16.60 ± 1.56** | **Erythema, burning, edema, hypopigmentation 3** |
| **HQ** |  | **5.30 ± 1.63** |  |
| **2009 Safoury OS[105]** | **TCA peel** | **20** | **38.25** | **Ⅲ or Ⅳ** | **10** | **2.19 ± 1.49** | **Swelling 2, erythema 5, discomfort 4, PIH 2, folliculitis/acne 5** |
| **TCA peel + Jessner peel** | **2.68 ± 1.34** | **Swelling 2, erythema 5, discomfort 16, folliculitis/acne 5** |
| 2008 Garg VK[106] | GA peel | 15 | 31.54 (17–45) | Ⅳ 28.6%，Ⅴ 71.4% | 12 | 3.76 ± 3.22 | Hyperpigmentation 20%, milia 26.6%, nodulocystic acne 5.5% |
| Tretinoin + GA peel | 17 | 4.28 ± 7.44 | Hyperpigmentation 14.3%, erythema and desquamation 53% |
| HQ + GA peel | 18 | 5.72 ± 6.72 | Hyperpigmentation 5.5%, erythema and desquamation 22%, persistent erythema 5.5% |
| 2002 Sarkar R[107] | GA peel + TCC | 20 | 31.45 (19–44) |  | 21 | 15.19 ± 5.88 | Erythema 20, PIH 2 |
| TCC | 20 | 31.05 (21–45) |  | 11.88 ± 4.70 | Erythema 8 |
| 1994 Candance K[108] | Tretinoin | 15 | 53 (44–67) | Epidermal 8; dermal 4; mixed 3 | 40 | 4.80 ± 7.33 | Erythema/Peeling 10 |
| Placebo | 13 | 52 (22–70) | Epidermal 5; dermal 7; mixed 3 | 1.60 ± 9.19 | Erythema/Peeling 1 |

\*25 Studies highlighted in boldface were split-face control studies.

**Abbreviation:** AA, Azelaic acid; AFL-CO2, ablative fractional laser-CO2 laser; AFL-Er:YAG, ablative fractional laser-Er:YAG laser; FbTc, fluocinolone-based combination cream; GA, glycolic acid; HA, hyaluronic acid; HQ, hydroquinone; IPL, intense pulsed light; KA, kojic acid; MN, microneedling; N, number of patients with treatment; NAFL, non-ablative fractional laser; oTA, oral tranexamic acid; PICO, picosecond laser; QSND, q-switch Nd:Yag 1064-nm laser; SA, salicylic acid; TCA, trichloroacetic acid; TCC, triple combination cream; tTA, topical tranexamic acid; tVC, topical vitamin C; PIH: post-inflammatory hyperpigmentation.

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