

SUPPLEMENTARY MATERIAL

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Combination treatment with monoclonal antibodies for the management of severe asthma and immune-mediated inflammatory diseases: a comprehensive review

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Supplementary Table 1. Combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, tezepelumab with a second biologic agent to treat dermatological immune-mediated inflammatory disease.

Author(s), year	Study type	Study population	Pathologies	Biologic Agents	Follow-up	Efficacy	Safety
Koç Yıldırım et al., 2023 [11]	Retrospective cohort study	n= 31 (19 F; 12 M; mean 45,13 yo)	CSU +PsO (n= 29); CSU+HS (n=2)	OMA+ADA (n=3) OMA+UST:(n=4) OMA+SEC:(n=17) OMA+IXE: (n=7)	2-45 mo (median 8 mo)	NA, but two pts stopped UST and IXE due to loss of response	One pt on SEC for PsO developed diarrhea after 9 mo, that resolved after the withdrawal of SEC.
Fougerousse et al., 2019 [12]	Retrospective observational study	28 yo F 35 yo F 25 yo F 60 yo F 51 yo M 49 yo M 53 yo F	CSU +PsO (n=6); Indolent systemic mastocytosis + PsO(n=1)	OMA+ ETA:(n=3) OMA+ IFX: (n=1) OMA+ ADA: n=2) OMA+ SEC: (n=1)	3-12 mo	UAS-7 decreased; no anaphylactic shocks in the patient with systemic mastocytosis	No AEs reported
Barry et al., 2019 [13]	Retrospective chart review	n=7 (3 F; 4 M; mean 61,3 yo)	AD+ PsO (n=6); BP+ PsO(n=1)	DUP+GUS: (n=7)	2-13 mo	Positive response to DUP in all six pts with AD. Positive response to GUS in 6/7 pts. Complete resolution of both AD and PsO in 1 pt.	Mild ISR in 1 pt.
Lommatzsch et al., 2022 [14]	Case series	70 yo F 63 yo M	Severe asthma + PsA (n=2)	ETA+BEN:(n=1) DUP+BRO:(n=1)	25 mo 16 mo	Shown data on asthma exacerbation, OCS use, asthma control and lung function	No AEs reported
Gerger et al, 2023 [15]	Case series	35 yo M 45 yo M	AD+ PsO	DUP+TIL: (n=1) DUP + BRO/TIL: (n=1)	NA	PASI 7.2 vs 11.9 at baseline for pt.1. For pt.2 PASI 3 vs 9.1 at baseline, EASI 9.4. TIL was introduced to reduce injection frequency	No significant AEs for pt.1. Conjunctivitis for pt.2
Diluvio et al., 2020 [16]	Case report	21 yo F	PsO+CSU	ADA+OMA	24 we	Reduction of the DLQI and complete reset of the UAS-7. OMA stopped after 24 we. 6 mo after discontinuation, the pt remained urticaria free	No AEs reported.
Karstarli Bakay et Kacar, 2022 [17]	Case report	56 yo F	PsO+CSU	SEC+OMA	6 mo	Clinical remission of urticaria	No AEs reported.

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Kabbani et al., 2022 [18]	Case report	49 yo F	PsO+PN	UST+DUP	4 y	Complete resolution of the pruritus after 3 mo and prurigo lesions completely cleared after 10 mo	No AEs reported.
Balestri et al., 2020 [19]	Case report	68 yo M	PsO and PsA+AD	SEC+DUP	15 mo	Benefit on articular pain and itch, improvement of cutaneous signs and symptoms	No AEs reported.
Mahar et al., 2021 [20]	Case report	40 yo F	PsO and PsA +severe asthma and CRSwNP	SEC+BEN/ SEC + DUP	8 mo with BEN 7 mo with DUP	PASI score 2.2 vs 15.2 at baseline; asthma and CRSwNP well controlled under DUP; ACQ5 decreased from 2 to 0.8; OCS dose reduced	Occasional sweating episodes and rhinorrhoea reported
Diluvio et al., 2022 [21]	Case report	35 yo F	PsO+CSU	TIL+OMA	6 mo	UAS-7 0 vs 40 at baseline	No AEs reported
Benko et al., 2022 [22]	Case report	57 yo M	PsO+CSU	UST/ADA/GUS +OMA	3 mo with UST; 3 mo with ADA; >21 mo with GUS	UAS-7 0 vs 17 after first dose of OMA. GUS led to PsO clinical remission	No AEs reported
Abdelmaksoud et al., 2023 [23]	Case report	58 yo F	PsO+CSU	SEC+OMA	6 mo	UAS7 decreased from 35 to 0, PASI decreased from 16.8 to 1	No AEs reported
Kaszycki et al., 2023 [24]	Case report	62 yo F	AD+PsO	DUP+GUS	1 y	Near-complete resolution of symptoms	No AEs reported

ACQ 5—Asthma Control Questionnaire 5; AD—atopic dermatitis; ADA—adalimumab; AEs- adverse events; BEN—benralizumab; BP- bullous pemphigoid; BRO-brodalumab; CRSwNP—chronic rhinosinusitis with nasal polyposis; CSU—chronic spontaneous urticaria; DLQI-dermatology life quality index; DUP—dupilumab; EASI-eczema area and severity index; EGPA—eosinophilic granulomatosis with polyangiitis; F—female; ETA-etanercept; GUS-guselkumab; HS- hidradenitis suppurativa; IFX-infliximab; ISR-injection site reaction; IXE-ixekizumab; M—male; MEP—mepolizumab; mo—months; NA—not available; OMA—omalizumab; OCS—oral corticosteroids; PASI-psoriasis area and severity index; PN-prurigo nodularis; PsA-psoriatic arthritis; PsO-Psoriasis; pt/pts-patient/patients; SEC-secukinumab; TIL-tildrakizumab; UAS-7- urticaria activity score 7; UST-ustekinumab; y—year; yo—year old; we—weeks.

Supplementary Table 2. Combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, tezepelumab with a second biologic agent to treat inflammatory bowel diseases.

Author(s), year	Study type	Study population	Pathologies	Biologic Agents	Follow-up	Efficacy	Safety
Spencer et al, 2023 [25]	Retrospective chart review	n=17 (9 M, 8 F; median 20 yo)	AD or anti-TNF-induced dermatitis + IBD	DUP + IFX (n=3) DUP +UST (n=5) DUP +VED(n=2)	0.13-4.8 y (median 1.2 y)	All 17 pts remained on DUP and had improvement in their dermatitis	No AEs reported
Fougerousse et al., 2019 [12]	Retrospective observational study	21 yo F 25 yo M	CSU+CD (n=1); CSU+ UC (n=1)	OMA+IFX: (n=1) OMA+ADA: (n=1)	4 mo 7 mo	UAS-7 decreased to 0, in one pt 30% decrease	No AEs reported
Malik et al., 2023 [26]	Case series	35 yo M	CD+ Severe asthma	IFX+OMA: (n=1)	36 mo	pt. 2 obtained full control of both diseases	No serious AEs reported
Lommatzsch et al., 2022 [14]	Case series	58 yo M 54 yo M	Severe asthma + UC (n=1); Severe asthma + CD (n=1)	VED+DUP:(n=1) MEP+UST: (n=1)	26 mo 6 mo	Shown data on asthma exacerbation, OCS use, asthma control and Lung function	No AEs reported
Gisoni et al., 2022 [10]	Case series	47 yo M	AD+CD (n= 1)	DUP+ADA: (n=1)	22 mo	NA	Arthralgia which resolved spontaneously within a few weeks
Alegre-Bailo et al, 2023 [27]	Case report	47 yo M	CD+AD	UST+ DUP	7 mo	After 7 months of DUP, SCORAD and EASI decreased to 0 (vs 71 and 40 at baseline, respectively). NRS for pruritus 1 vs 9 and NRS for sleep 0 vs 6	No AEs reported
Patel et al., 2016 [28]	Case report	25 yo F	HES + UC	MEP+IFX	6 mo	Abdominal pain, diarrhea, incontinence, bloody stools and QoL improved. OCS stopped	Headaches and worsened anxiety, C.Difficile infection

AD—atopic dermatitis; ADA—adalimumab; AEs—adverse events; CD—Crohn Disease; CSU—chronic spontaneous urticaria; DUP—dupilumab; EASI—eczema area and severity index; F—female; HES—hypereosinophilic syndrome; IBD—inflammatory bowel disease; IFX—infliximab; ISR—injection site reaction; M—male; MEP—mepolizumab; mo—months; NA—not available; NRS-numeric rating scale; OMA—omalizumab; OCS—oral corticosteroids; pt/pts-patient/patients; QoL—quality of life; SCORAD-SCORing Atopic Dermatitis; UAS-7—urticaria activity score 7; UC—ulcerative colitis; UST-ustekinumab; y—year; yo—year old; VED—vedolizumab.

Supplementary Table 3. Combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, tezepelumab with a second biologic agent to treat rheumatoid arthritis.

Author(s), year	Study type	Study population	Pathologies	Biologic Agents	Follow-up	Efficacy	Safety
Lommatzsch et al., 2022 [14]	Case series	66 yo F 66 yo F	Severe asthma + RA (n=2)	ETA+BEN: (n=1) MEP+RIT: (n=1)	33 mo 24 mo	Shown data on asthma exacerbation, OCS use, asthma control and Lung function	No AEs reported
Gisondi et al., 2022 [10]	Case series	82 yo M	AD+RA (n=1)	DUP+ABA: (n=1)	15 mo	NA	No AEs reported
Malik et al., 2023 [26]	Case series	56 yo F 62 yo F	RA+Severe asthma (n=2);	ETA+MEP: (n=1) OMA+ETA:(n=1)	24 mo 36 mo	DAS28 2.27 vs 6.25 for Pt. 1. Pt. 3 obtained full control of both diseases	No serious AEs reported
Takeuchi et al., 2022 [29]	Case report	72 yo F	RA+CSU	TOC+OMA	NA	RA well-controlled. Improvement of UCT score (16 vs 10 at baseline) after 1 mo. OMA treatment stopped after 12 doses and 12 mo after discontinuation, the pt. remained urticaria-free	No AEs reported
Yamada et al., 2019 [30]	Case report	69 yo M	Severe asthma + RA	BEN+GOL	4 mo	DAS28-CRP 1.15 vs 4.74 at baseline, FEV ₁ improved to 80%; FeNO decreased to 31 ppb; ACT score improved (22 vs 19)	No AEs reported
Ghazanfar and Thomsen, 2019 [31]	Case report	64 yo F	RA+CSU	ETA+OMA	3 mo	Decreased UAS-7 (7 vs 28); improvement in UCT (11 vs 1) and DLQI (0 vs 2)	No AEs reported

ABA-abatacept; ACT-Asthma Control Test; AD—atopic dermatitis; AEs- adverse events; BEN—benralizumab; CSU—chronic spontaneous urticaria; DAS28-CRP- Disease Activity Score 28 with CRP; DLQI-dermatology life quality index; DUP—dupilumab; ETA-etanercept; F—female; FeNO- fractional exhaled nitric oxide ; FEV₁- forced expiratory volume in 1 s; GOL-golimumab; M—male; MEP—mepolizumab; mo—months; NA—not available; OMA—omalizumab; OCS—oral corticosteroids; pt/pts-patient/patients; RA-Rheumatoid Arthritis; RIT-rituximab; TOC-tocilizumab; UAS-7- urticaria activity score 7; UCT- urticaria control test; yo— year old.

Supplementary Table 4. Combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, tezepelumab with a second biologic agent to treat ankylosing spondylitis.

Author(s), year	Study type	Study population	Pathologies	Biologic Agents	Follow-up	Efficacy	Safety
Fougerousse et al., 2019 [12]	Retrospective observational study	29 yo M	CSU+AS (n=1)	OMA+ETA:(n=1)	9 mo	UAS-7 decreased	No AEs reported
Lommatzsch et al., 2022 [14]	Case series	40 yo F	Severe asthma +AS (n=1)	DUP+ETA: (n=1)	36 mo	Shown data on asthma exacerbation, OCS use, asthma control and Lung function	No AEs reported
Gisondi et al., 2022 [10]	Case series	46 yo M	AD+AS (n=1)	DUP+SEC (n=1)	18 mo	NA	No serious AEs reported.

AD—atopic dermatitis; AEs- adverse events; AS- ankylosing spondylitis; CSU—chronic spontaneous urticaria; DUP—dupilumab; F—female; ETA-etanercept; M—male; mo—months; NA—not available; OMA—omalizumab; OCS—oral corticosteroids; pt/pts-patient/patients; SEC-secukinumab; UAS-7- urticaria activity score; yo—year old.

Supplementary Table 5. Other combinations of asthma-approved biologics with monoclonal antibodies of different nature with their respective indications, not suitable for inclusion in previous groups.

Author(s), year	Study type	Study population	Pathologies	Biologic Agents	Follow-up	Efficacy	Safety
Steinhoff et al., 2021 [32]	Case report	38 yo M	AD+ Recalcitrant erythrodermic ichthyosis	DUP+GUS	80 we	Improvement of erythrodermic ichthyosis and eczema	No AEs reported
Gisondi et al., 2022 [10]	Case series	68 yo F 62 yo M	AD+HCL (n= 2)	DUP+ EVO: (n= 2)	3 mo 12 mo	NA	No AEs reported
Lommatzsch et al., 2022 [14]	Case series	60 yo F 44 yo F 57 yo F	Severe asthma + OP(n=1); Severe asthma + EGPA+ OP (n=1); Severe asthma+TRAPS+ HCL (n=1)	BEN+DEN:(n=1); BEN+DEN+RIT: (n=1); DUP+CAN+ALI: (n=1)	18 mo 18 mo 24 mo	Shown data on asthma exacerbation, OCS use, asthma control and Lung function	No AEs reported
Le et al, 2024 [33]	Retrospective chart review	n=10 (7 F; 3 M; (median 62 y)	BP	RIT+OMA: (n=10)	5-45 mo	High dose RIT- OMA cohort achieved complete remission. All pts in the Low dose RIT- OMA group improved but none achieved complete remission	Mild AEs reported
Kwon et al, 2023 [34]	Retrospective chart review	n=17 (8 M: 9 F; median age 79 yo)	BP	RIT+OMA: (n=17)	median 0.3 y	RIT+OMA group showed shorter time to disease control and lower corticosteroid dose	No severe AEs reported
Afiari et al, 2020 [35]	Case report	55 yo F	EGPA	MEP+RIT	NA	Improvement in renal function, wheezing and congestion. The pt. returned to work	NA
Mutoh et al, 2022 [36]	Case report	45 yo M	EGPA	MEP+RIT	NA	The pt. achieved remission. The OCS dose was tapered. BVAS decreased to 0	No AEs reported.

AD—atopic dermatitis; AEs- adverse events; ALI-alirocumab; BEN—benralizumab; BP- bullous pemphigoid; BVAS- Birmingham Vasculitis Activity Score; CAN-canakinumab; DEN-denosumab; DUP—dupilumab; EGPA—eosinophilic granulomatosis with polyangiitis; EVO-evolocumab; F—female; GUS-guselkumab; HCL-hypercholesterolemia; M—male; MEP—mepolizumab; mo—months; NA—not available; OMA—omalizumab; OCS—oral corticosteroids; OP- Osteoporosis; Pt/pts-patient/patients RIT-rituximab; TRAPS-; y—year; yo—year old; we—weeks.