Ηωσινοφιλική κοκκιωμάτωση με πολυαγγειίτιδα – Νέες θεραπευτικές επιλογές

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EGPA

Κλινικά χαρακτηριστικά

Θεωρείται σαν να έχει 3 φάσεις (δεν παρατηρείται σε όλους τους ασθενείς, συχνά δεν συμβαίνει διαδοχικά)

- Πρόδρομη φάση: άσθμα, αλλεργική ρινίτιδα
- Ηωσινοφιλική φάση: περιφερική εωσινοφιλία, διηθήσεις EOS σε ιστούς
- Αγγειιτιδική φάση: νεύρα, δέρμα, πνεύμονες, πεπτική οδός, καρδιά

1990 ACR Criteria for EGPA Classification

A vasculitis can be classified EGPA if 4 of the findings are present

- **Asthma**
- **Eosinophilia *> 10% of differential white blood cell count***
- **Mononeuropathy (including multiplex) or polyneuropathy**
- **Nonfixed pulmonary infiltrates on roentgenography**
- **Paranasal sinus abnormality**
- **Extravascular eosinophils revealed at biopsy**
- **Biopsy containing a blood vessel with extravascular Eosinophils**

Sensitivity 85%, specificity of 99.7%

Ηωσινοφιλική κοκκιωμάτωση με πολυαγγειίτιδα (EGPA)

2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

Ορισμός: Νεκρωτική κοκκιωματώδη φλεγμονή πλούσια σε EOS συχνά προσβάλλουσα την αναπνευστική οδό, και νεκρωτική αγγειίτιδα μικρών και μεσαίου μεγέθους αγγείων σχετιζόμενη με άσθμα και ηωσινοφιλία.

- Συχνά ρινικοί πολύποδες
- ANCA+ συχνότερα σε σπειραματονεφρίτιδα
- Μπορεί να συμμετέχει μόνο η αναπνευστική οδός
- Συχνά κοκκιωμάτωδη και μη- κοκκιωματώδη εξωαγγειακή φλεγμονή πλούσια σε EOS (μυοκάρδιο, πνεύμονες, πεπτικό)

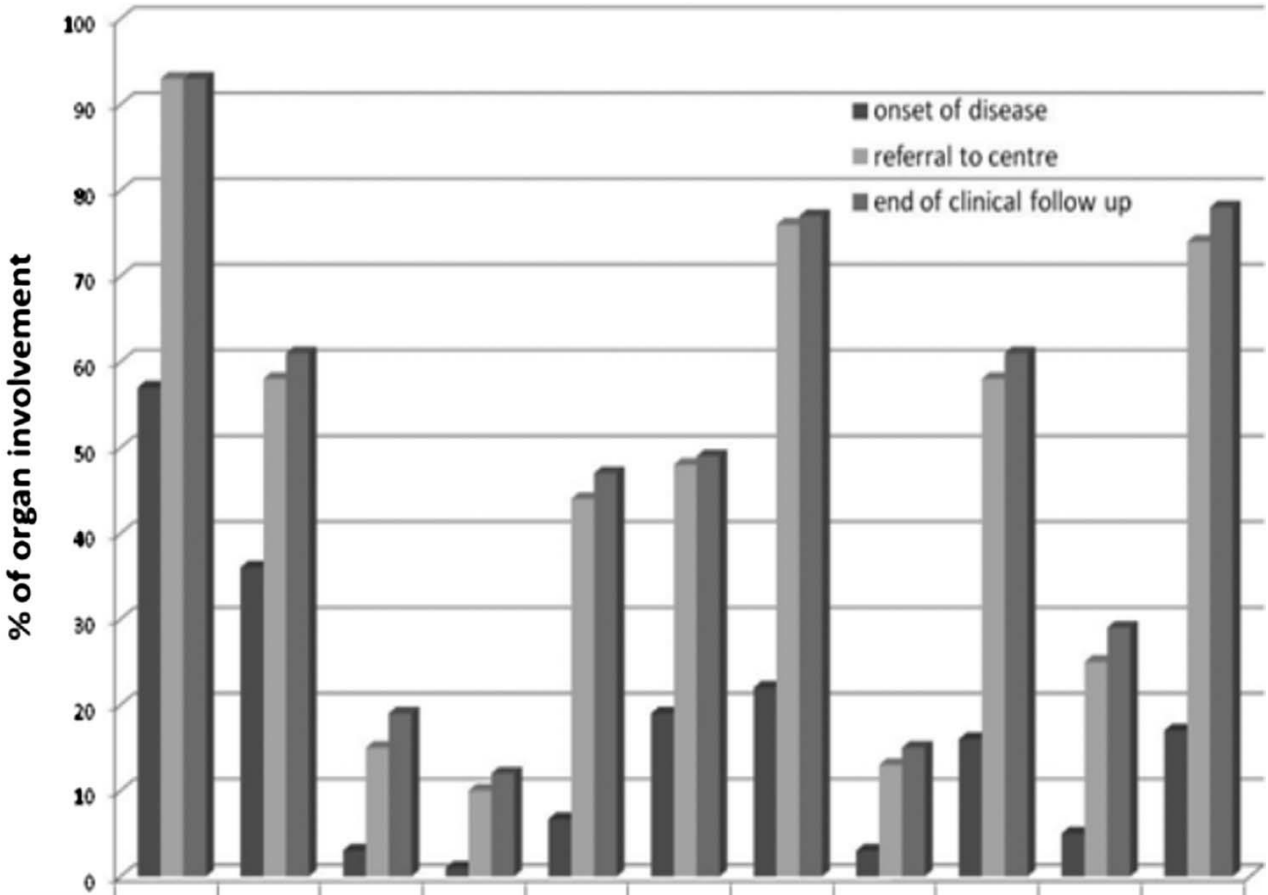
A&R 2013

CHCC2012 nomenclature and definitions do not provide diagnostic and classification criteria, but provide a framework for inferring and rigorously verifying such criteria

Term	Explanation
Diagnosis	The name of a disease
Definition	Disease processes present in any patient that justify assignment of the diagnosis (name)
Classification criteria	Observations that classify a specific patient into a standardized category for study
Diagnostic criteria	Observations that demonstrate or confidently predict the presence of the defining features of the disease in a specific patient

EGPA

Προσβολή οργάνων-συστημάτων



	E	L	K	Ey	H	S	P	C	A	Gi	B
onset of disease	57	36	3	1	7	19	22	3	16	5	17
referral to centre	93	58	15	10	44	48	76	13	58	25	74
end of clinical follow up	93	61	19	12	47	49	77	15	61	29	78

A, joints; B, constitutional symptoms; C, central nervous system; E, ENT tract; Ey, Eye; Gi, gastrointestinal tract; H, heart; K, kidney; L, lung; P, peripheral nervous system; S, skin

ARD 2013

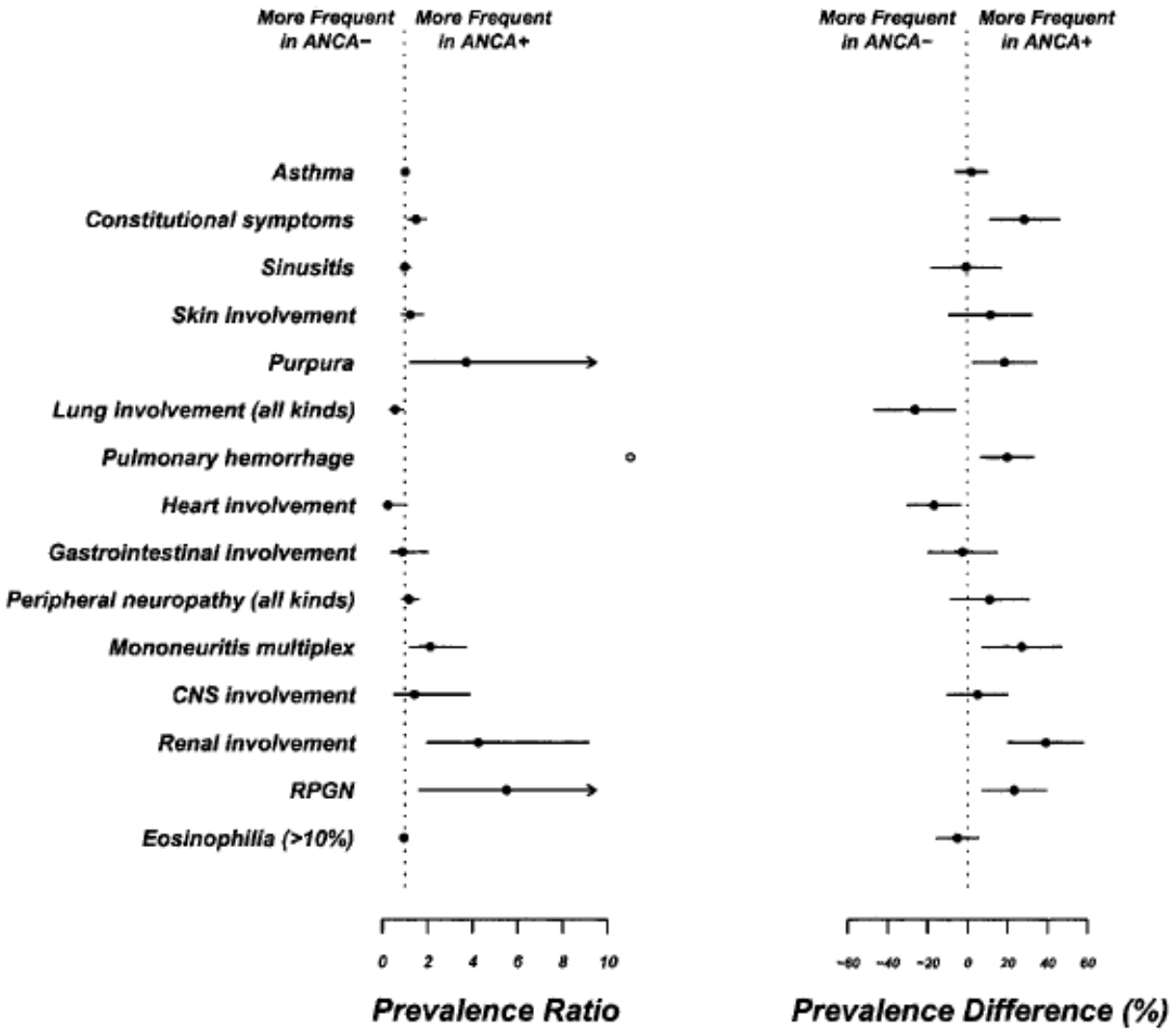
EGPA

Different Phenotypes

- EGPA is increasingly considered a syndromic condition of several clinically or pathogenetically distinct subgroups

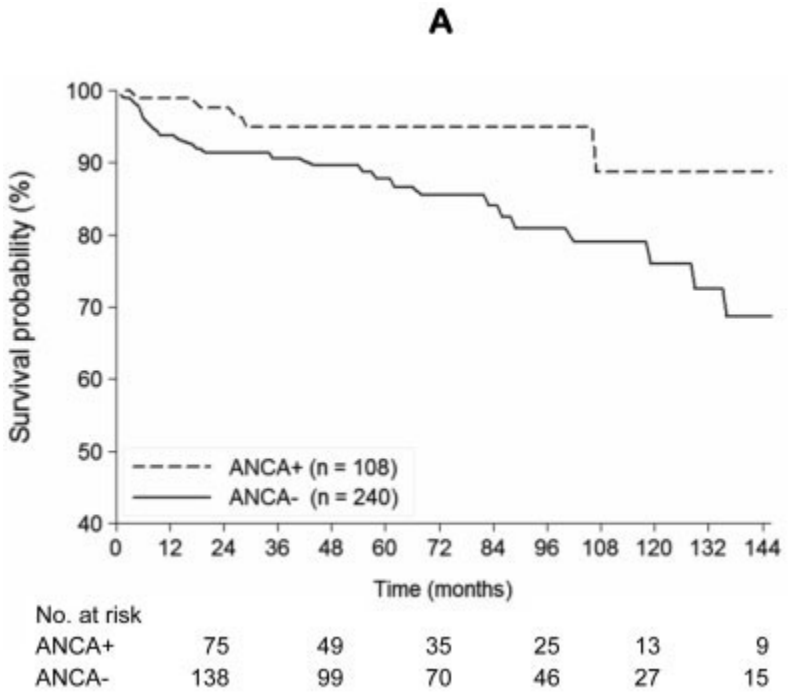
- The most plausible subclassification contrasts ANCA-positive and ANCA-negative

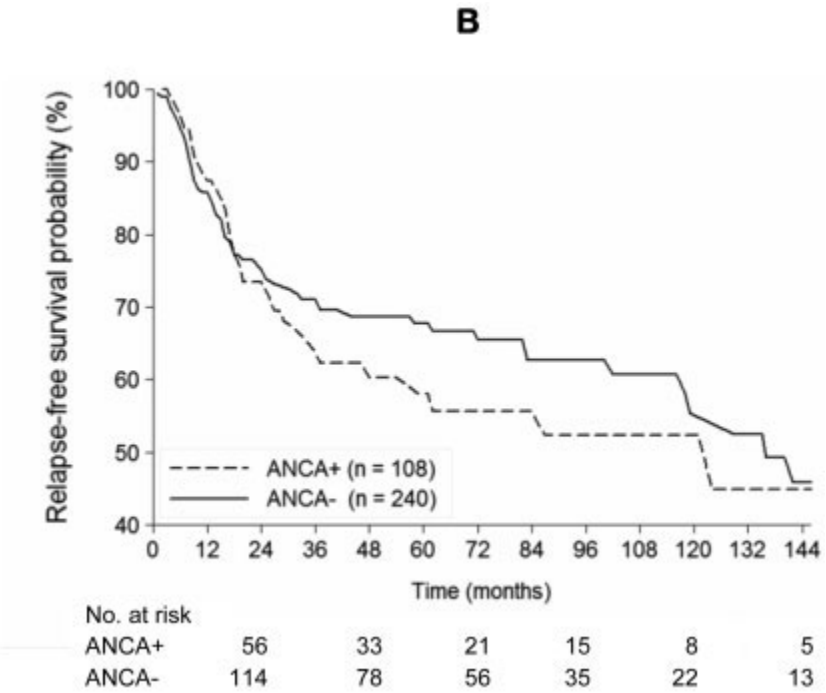
Comparisons of the Clinical Characteristics Seen in Either Subgroup Showed Significant Differences



A&R 2005

Long-Term Followup of the 383 Patients Enrolled in the French Vasculitis Study Group Cohort





A&R 2013

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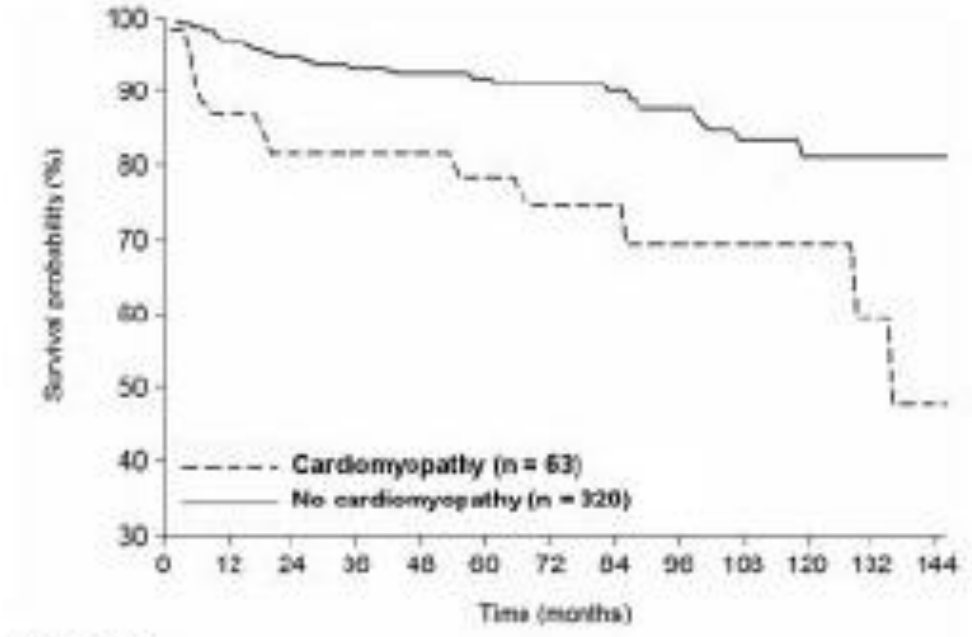


A&R 2013

Prognostic Factors for EGPA

TABLE 4. Mortality associated with the five-factors score (FFS)*

FFS	Dead (%)	Alive (%)	Relative Risk	No. of Patients
0	11.9	88.1	0.62	218
1	25.9	74.1	1.35	81
2	45.95	54.05	2.40	37
Total	64	272		336†

* The 5 prognostic factors are cardiomyopathy, CNS involvement, severe GI tract symptoms, renal failure (i.e., Cr > 1.58 mg/dL), high proteinuria (>1 g/d). FFS = 0 when all 5 factors are absent; FFS = 1 when only 1 factor is present; FFS = 2 when 2 or more factors are present.

Five-factor score in eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

1996 five-factor score[1]	Revised 2011 five-factor score[2]
Cardiac involvement	Age >65 years
Gastrointestinal disease (bleeding, perforation, infarction, or pancreatitis)	Cardiac insufficiency
Renal insufficiency (plasma creatinine concentration >1.6 mg/dL [141 mmol/L])	Renal insufficiency (stabilized peak creatinine 1.7 mg/dL [150 micromol/L])
Proteinuria (>1 g/day)	Gastrointestinal involvement
Central nervous system involvement	Absence of ENT manifestations (presence is associated with a better prognosis)

The presence of each factor is given one point. The FFS score ranges from 0 to 2: a score of 0 is given when none of the factors is present, a score of 1 for one factor, and a score of 2 for two or more factors.

FFS: five-factor score; ENT: ear, nose, and throat.

EGPA

Έκβαση

Guillevin et al. Medicine 1996;75:17

- 342 patients (119 PAN no HBV, 89 PAN + HBV, 52 MPA, 82 EGPA)
- Five Factor Score (FFS)
  - Cardiac involvement
  - Gastrointestinal disease (bleeding, infarction, perforation)
  - Renal insufficiency (creatinine >1.6 mg/dL [141 mmol/L])
  - Proteinuria (>1 g/day)
  - CNS involvement

Guillevin et al. Medicine 1999;78:26

- 96 patients with EGPA
- Overall mortality – 23 deaths
  - 12% FFS = 0 versus 38% FFS > 2
- Myocardial involvement was the most frequent cause of death
  - responsible for 9 of 23 deaths (39.1%)

EGPA

Θεραπεία

Limited information on EGPA as an isolated entity

Most data comes from grouping with other diseases:

- ANCA-associated vasculitis- combined with GPA and MPA
- Combined series with PAN and MPA

Treatment strategy based upon manifestations and disease severity

Glucocorticoids

- effective alone for none severe EGPA (*Ribi et al. A&R 2008;58:586)*
- asthma often limits tapering

Cytotoxic therapy

- Cyclophosphamide should be utilized for life-threatening disease involving the GI tract, CNS, glomerulonephritis, heart (FFS >0) *(Gayraud et al. Arthritis Rheum 2001, Guillevin et al Medicine 1999)*

Treatment of EGPA Without Poor-Prognosis Factors (FFS=0)

A Multicenter, Prospective, Randomized, Open-Label Study of 72 Patients

- 93% achieved remission with CS therapy alone
- 35% relapsed, mainly during the first year of treatment
- Among the 19 patients randomized to additional immunosuppression because of treatment failure or relapse, 5 of 10 receiving AZA and 7 of 9 receiving pulse CYC achieved remission
- Survival rates in all patients at 1 and 5 years were 100% and 97%, respectively
- 79% of the patients whose disease was in remission required low dose CS therapy, mainly to control respiratory disease
- CS-related adverse events were observed in 31% of the 72 patients

A&R 2008

The EGPA Consensus Task Force Recommendations

Disease Activity

- No reliable biomarker to measure EGPA activity.
- Definition of disease remission: the absence of a clinical systemic manifestation (excluding asthma and/or ENT)
- Definition of relapse: the new appearance or recurrence or worsening of clinical EGPA manifestation(s) (excluding asthma and/or ENT) requiring the addition, change or dose increase of GC and/or IS
- ENT manifestations and/or asthma flares may not necessarily reflect vasculitis activity and that these symptoms should be monitored separately.

Eur J Inter Med 2015

The EGPA Consensus Task Force Recommendations

Treatment

Use of glucocorticoids is appropriate to achieve EGPA remission; the dose prescribed should be ~1 mg/kg/day prednisone for patients with organ- or life-threatening manifestations (A)

Patients with life and/or organ-threatening disease manifestations (i.e., heart, GI, central nervous system, severe peripheral neuropathy, severe ocular disease, alveolar hemorrhage and/or glomerulonephritis) should be treated with a remission-induction regimen combining glucocorticoids and an additional immunosuppressant (e.g. cyclophosphamide) (B)

Maintenance therapy (with azathioprine or methotrexate) is recommended for patients with life- and/or organ-threatening disease manifestations after a remission-induction therapeutic regimen (C)

Eur J Inter Med 2015

The EGPA Consensus Task Force Recommendations

Treatment

Glucocorticoids alone may be suitable for patients without life and/ or organ-threatening disease manifestations; additional immunosuppression can be considered for selected patients for whom the prednisone dose cannot be tapered to 7.5 mg/day after 3–4 months of therapy or patients with recurrent disease (C)

IVIg can be considered a second-line therapy for patients on glucocorticoids (and/or other immunosuppressants) with EGPA flares refractory to other treatments or during pregnancy; in the context of drug-induced hypogammaglobulinemia with severe and/or recurrent infections, Ig-replacement may be considered (C)

Eur J Inter Med 2015

Adding AZA to Remission-Induction GCs for EGPA, MPA, or PAN Without Poor Prognosis Factors

A Randomized, Controlled Trial

Table 1. Baseline characteristics of the patients randomized to receive AZA or placebo*

	AZA (n = 46)	Placebo (n = 49)	Total (n = 95)
Age, mean ± SD years	53.7 ± 16.9	60.8 ± 16.3	57.3 ± 16.9
Sex, male	26 (56.5)	24 (49)	50 (52.6)
Vasculitis type			
EGPA	25 (54.3)	26 (53.1)	51 (53.7)
MPA	9 (19.6)	16 (32.7)	25 (26.3)
PAN	12 (26.1)	7 (14.3)	19 (20)

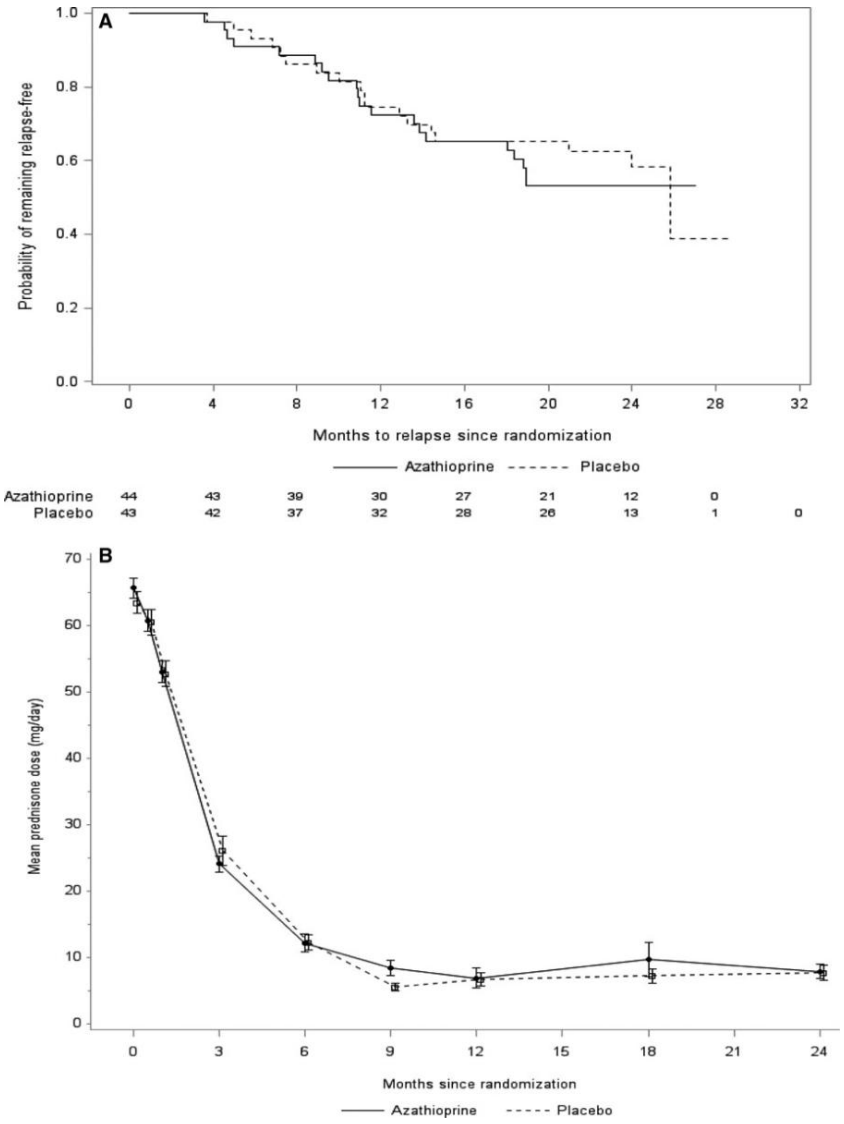
Table 3. Patient outcomes according to SNV stratification*

Outcome	AZA	Placebo
Patients with EGPA		
No. of patients	25	26
Primary end point: remission induction failures and relapses at month 24†	12/25 (48)	12/26 (46.2)
Secondary end points		
Initial remission	25/25 (100)	25/26 (96.2)
Major relapses at month 24	4/25 (16)	3/24 (12.5)
Minor relapses at month 24	7/25 (28)	7/24 (29.2)
Unclassified relapses	1/25 (4)	0/24 (0)
Any relapse (minor, major, or unclassified)	12/25 (48)	10/24 (41.7)
Asthma/rhinosinusitis exacerbations§	6/25 (24)	5/26 (19.2)

A&R 2017

Adding AZA to Remission-Induction GCs for EGPA, MPA, or PAN Without Poor Prognosis Factors

A Randomized, Controlled Trial



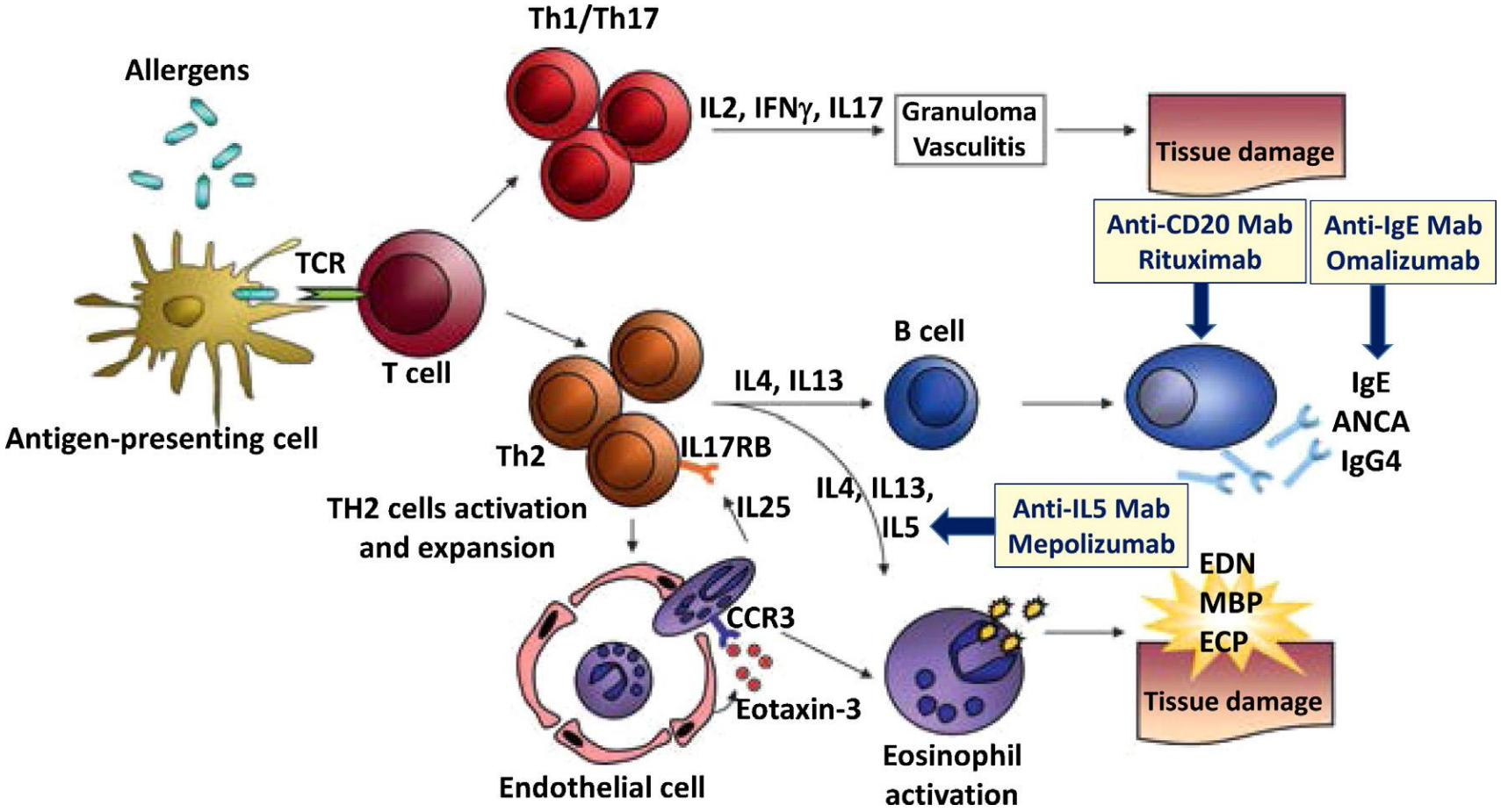
A&R 2017

EGPA

Ανεκπλήρωτες ανάγκες θεραπείας

- Not all patients respond to steroids initially /Steroids alone don’t work (add-on therapy)
- Pt relapses on low dose steroids → even if bump up steroid dose → Steroids can’t be tapered (step-down therapy)
- Very few patients get off steroids
- Side effects

Pathogenesis of EGPA and therapeutic targets



Γιατί anti-IL5?

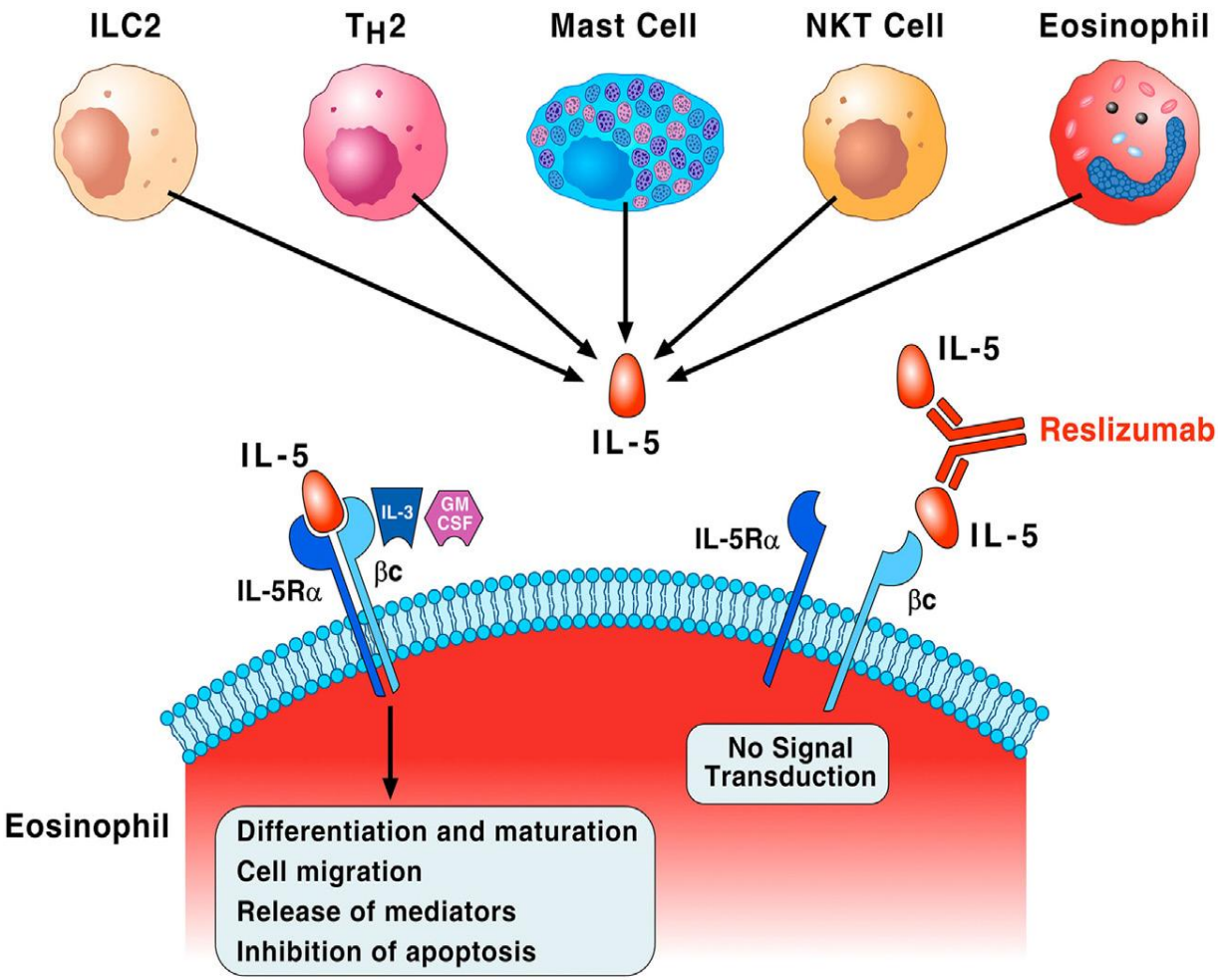
IL-5 has a role in Regulating Eosinophils

IL-5 cytokine regulates:

- Bone marrow release of eosinophils
- Eosinophil tissue survival
- Eosinophil activation

IL-5 is present at increased levels in patients with EGPA

IL-5


ILC2
TH2
Mast Cell
NKT Cell
Eosinophil
IL-5
IL-5
Reslizumab
IL-5
IL-3
GM CSF
IL-5Rα
βc
IL-5Rα
IL-5
βc
No Signal Transduction
Eosinophil
Differentiation and maturation
Cell migration
Release of mediators
Inhibition of apoptosis

Anti-IL5

Mepolizumab (approved by FDA)

Reslizumab

Benralizumab

Mepolizumab

Fully humanized, anti-IL-5 monoclonal IgG1 antibody

Binds to IL-5 with high affinity and specificity

- Prevents IL-5 associating with the IL-5 receptor α-chain on the eosinophil surface

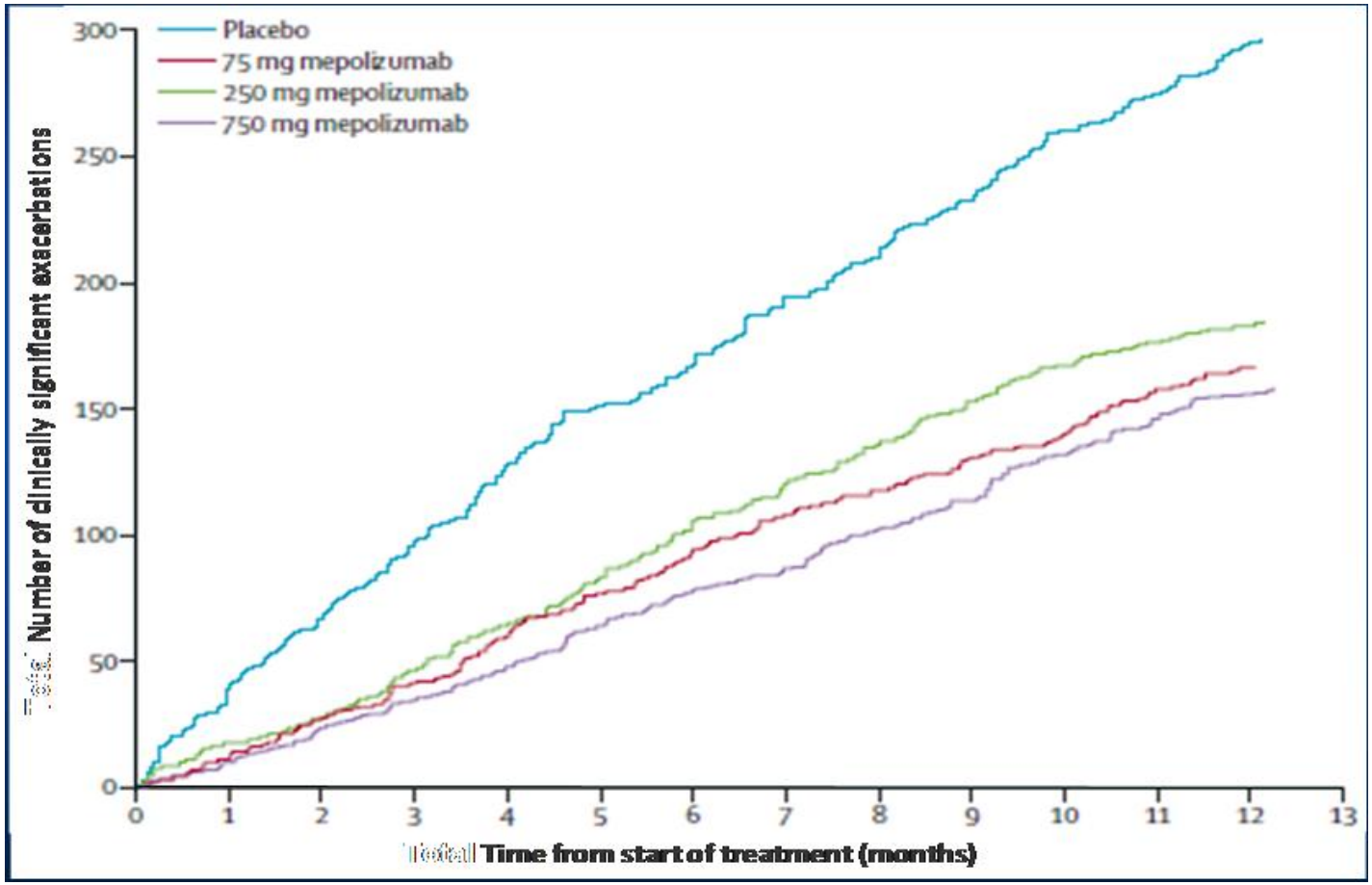
Consistently reduces eosinophil numbers in hypereosinophilic states

Mepolizumab has been studied in eosinophilic diseases

Mepolizumab has been evaluated in pilot studies with evidence for efficacy in:

- **Eosinophilic gastrointestinal disease**
- **Hypereosinophilic syndrome (HES)**
- **Effective in decreasing steroid dose for HES in randomized double blind placebo controlled trial (Rothenberg, NEJM 2008)**

Mepolizumab reduces exacerbations vs. placebo in Eosinophilic Asthma



Υπόθεση

Compared with placebo, anti-IL5 therapy would safely provide EGPA patients with a novel steroid-sparing treatment option that would reduce exacerbations, decrease serum markers of disease activity and allow for safe corticosteroid tapering (as add-on therapy)

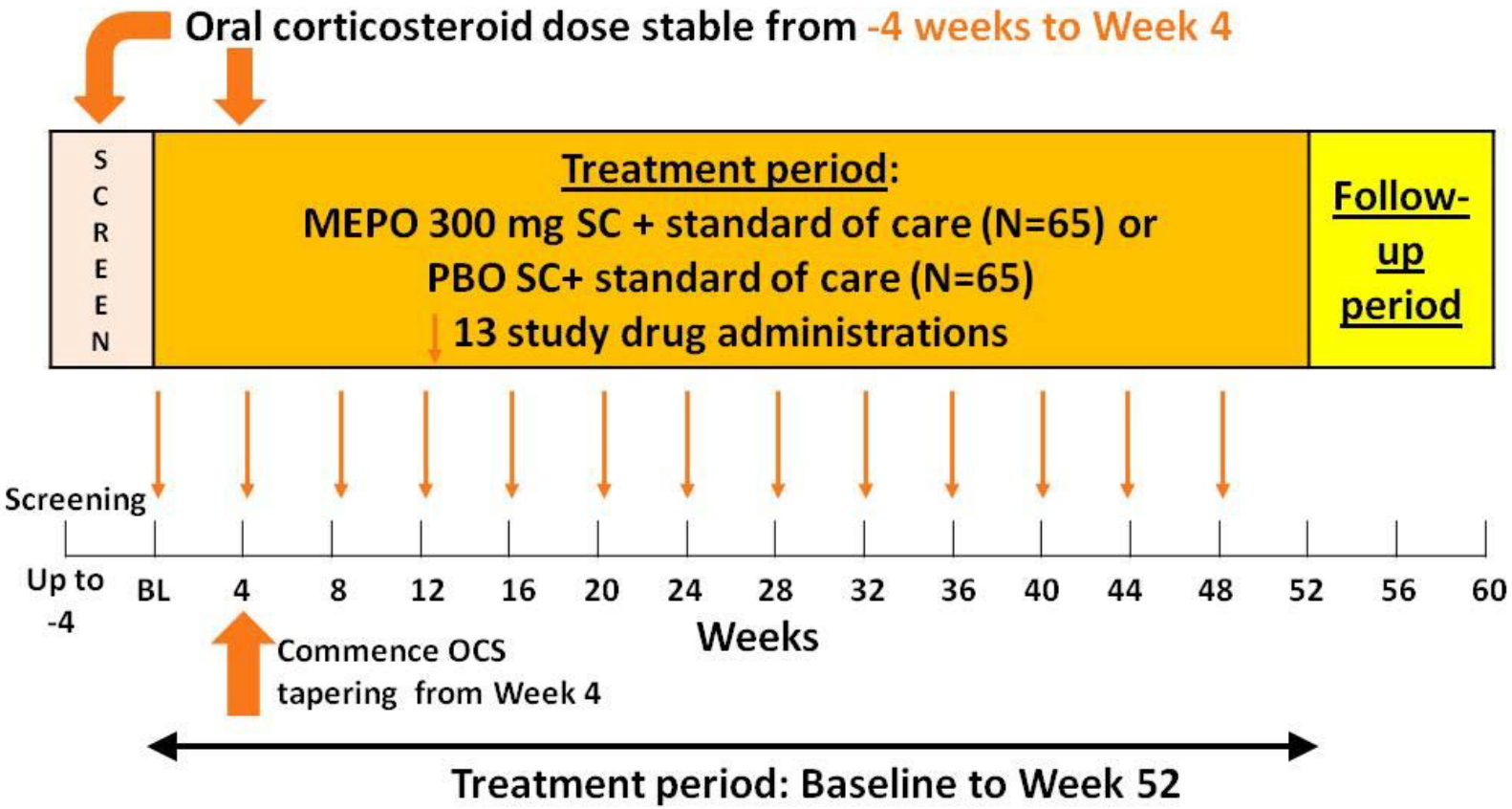
MIRRA study

Mepolizumab Treatment **I**n **R**elapsing or **R**efractory EGP**A**

NEJM 2017

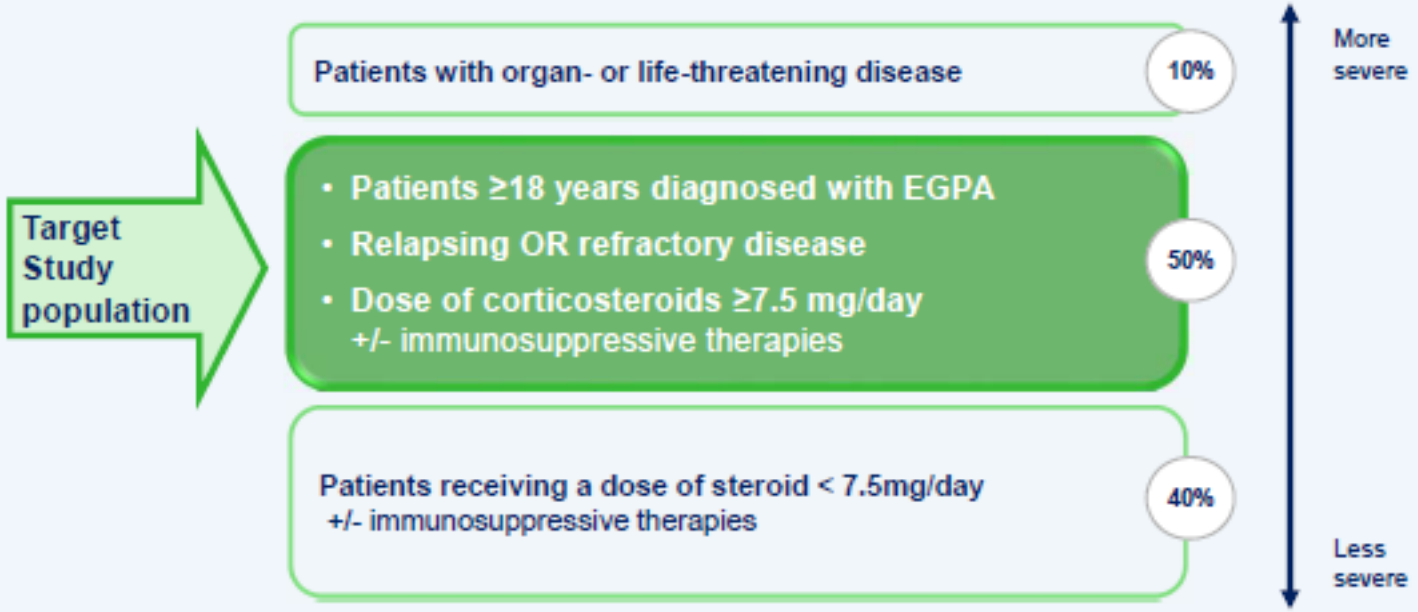
MIRRA study

Σχεδιασμός



Target population n=130

The population most likely to benefit from treatment with mepolizumab are patients with a history of relapsing or refractory disease AND receiving a dose of OGC ≥ 7.5mg/day



Relapsing: history of at least 1 relapse within the past 2 years whilst receiving a dose of prednisolone (or equivalent) of ≥ 7.5 mg/day

Refractory: failure to attain remission (BVAS=0 and steroid dose ≤7.5mg/day for 4 weeks, i.e. EULAR) following induction treatment with a standard regimen (e.g. corticosteroids, CYC, AZA, MTX or MMF) for at least 3 months OR within the past six months, an inability to taper OGCs to below 7.5mg/day due to the reoccurrence of symptoms of EGPA

Key inclusion criteria

- ☑ EGPA diagnosis for at least 6 months based on the history or presence of asthma plus eosinophilia (>1.0x10^9/L and/or >10% of leucocytes)

Plus

At least two additional features of EGPA:

- a biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration or eosinophil-rich granulomatous inflammation;
- neuropathy, mono or poly (motor deficit or nerve conduction abnormality);
- pulmonary infiltrates, non-fixed;
- sino-nasal abnormality;
- cardiomyopathy (established by echocardiography or MRI);
- glomerulonephritis (haematuria, red cell casts, proteinuria);
- alveolar haemorrhage (by bronchoalveolar lavage);
- palpable purpura;
- ANCA positive (MPO or PR3)

- ☑ History of relapsing OR refractory disease

MIRRA study

Relapsing/Refractory disease

Relapsing disease: Participant must have a past history of at least one confirmed EGPA relapse (i.e., requiring increase in CS dose, initiation/increased dose of immunosuppressive therapy or hospitalisation) within the past 2 years which occurred at least 12 weeks prior to screening (Visit 1) while receiving a dose of prednisolone (or equivalent) of ≥7.5 mg/day.

Refractory disease: failure to attain remission (BVAS=0 and CS dose ≤7.5 mg/day) within the prior 6 months following induction treatment with a standard regimen, administered for at least 3 months

Key inclusion criteria (cont.)

- ☑ Corticosteroid therapy:
  - Stable dose of prednisolone or prednisone ≥7.5 mg/day*, <50 mg/day for at least 4 weeks prior to Baseline

- ☑ Immunosuppressive therapy:
  - If receiving immunosuppressive therapy (excluding cyclophosphamide) the dosage must be stable for the 4 weeks prior to Baseline and during the study (dose reductions for safety reasons will be permitted)

MIRRA study

Exclusion criteria

Organ–threatening EGPA: organ-threatening EGPA as per EULAR criteria, i.e., organ failure due to active vasculitis, creatinine >5.8 g/dL

Life–threatening EGPA

- Intensive care required
- Severe alveolar hemorrhage or hemoptysis requiring transfusion or ventilation
- Rapidly progressive glomerulonephritis with creatinine >2.5 mg/dL or rise

in creatinine >2 mg/dL over a 48-hour period.

- Severe gastrointestinal involvement
- Severe central nervous system involvement
- Severe cardiac involvement, for example, life-threatening arrhythmia, cardiac failure

MIRRA study

Καταληκτικά σημεία

Πρωτεύοντα:

1. Total accrued duration of remission over the 52 week study treatment period reported as proportion of subjects achieving remission
2. The proportion of subjects who are in remission at both Weeks 36 and 48 of the study treatment period.

Remission was defined as a BVAS of 0 and the receipt of prednisolone < 4.0 mg or less per day over the 52-week period.

MIRRA study

Καταληκτικά σημεία

Δευτερεύοντα:

1. Time to first confirmed EGPA relapse. (Relapse was defined as any of the following categories: active vasculitis (BVAS >0), active asthma symptoms or signs with a corresponding worsening in the score on the Asthma Control Questionnaire,

version 6 (ACQ-6; range, 0 to 6 points), or active nasal or sinus disease with a corresponding worsening in at least one of the sinonasal-symptom items leading to one of the following: an increase in the glucocorticoid dose to more than 4.0 mg per day of prednisolone (or equivalent), an initiation of or increase in immunosuppressive therapy, or hospitalization.

2. Average daily prednisolone/prednisone dose during the last 4 weeks of the study treatment period (48 through 52)

3. Proportion of subjects in each treatment group who achieve remission within the first 24 weeks of the study and then remain in remission for the remainder of the study treatment period.

4. Άλλα [Absolute eosinophil count, Lung function (FEV1), Asthma Symptom score (ACQ), Safety Metrics]

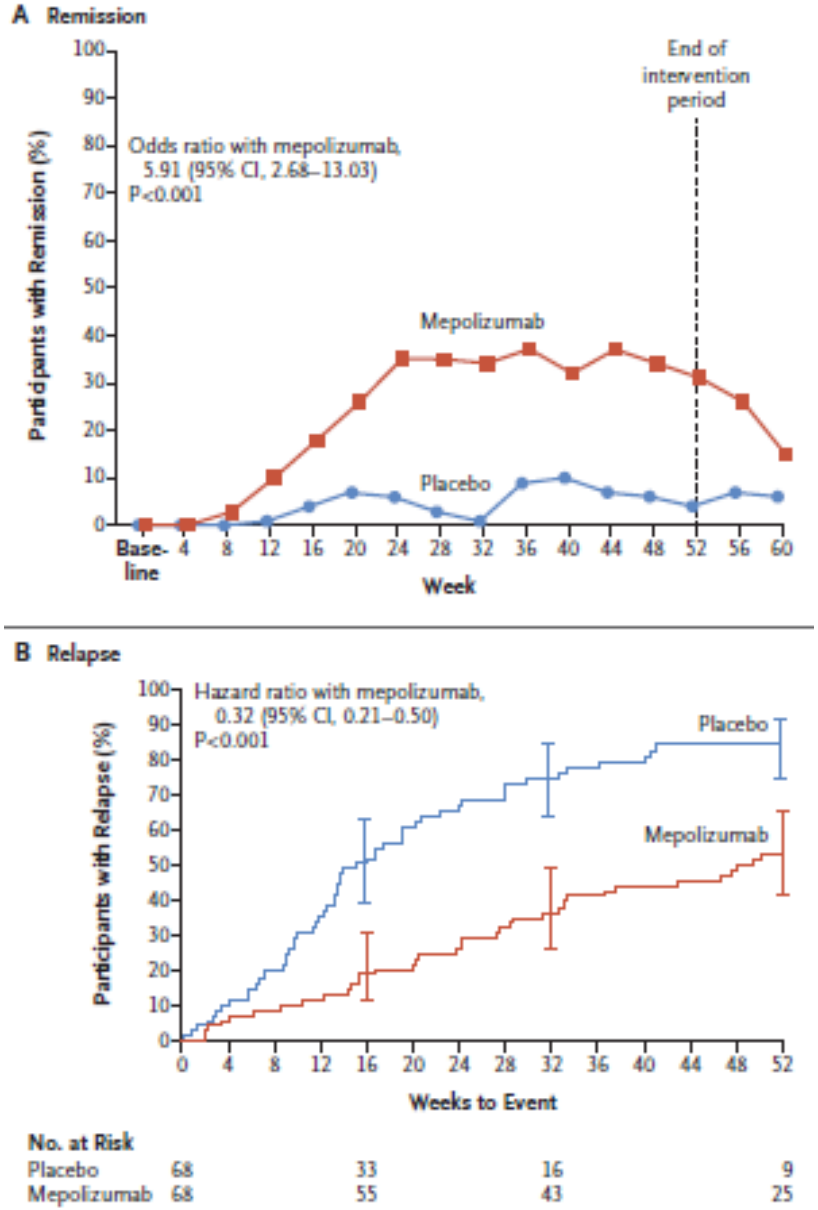
MIRRA study

Χαρακτηριστικά ασθενών

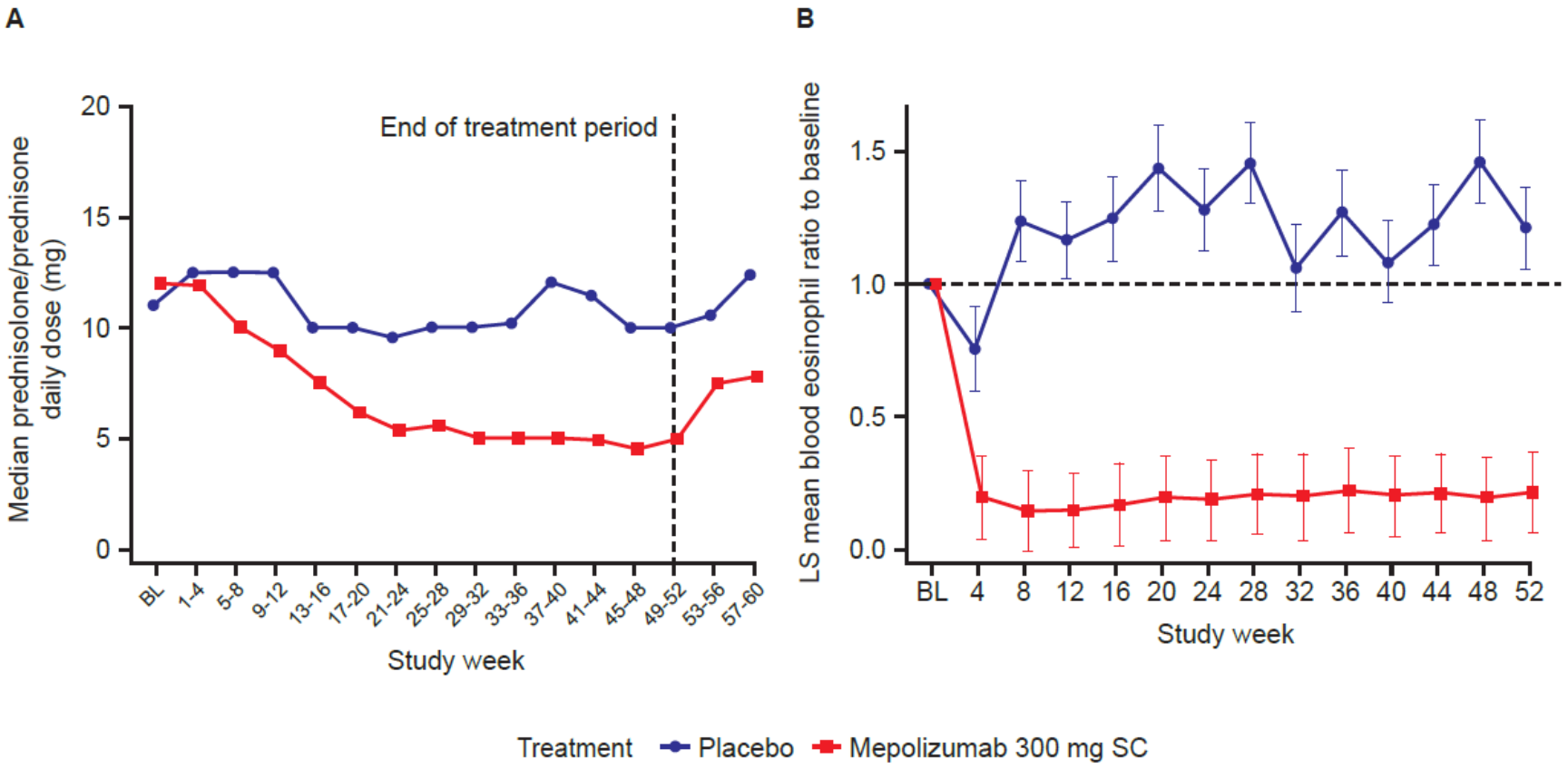
Characteristic	Mepolizumab (N=68)	Placebo (N=68)
Age — yr	49±12	48±14
Male sex — no. (%)	26 (38)	30 (44)
ANCA-positive status — no. (%)†	7 (10)	6 (9)
Absolute eosinophil count per cubic millimeter‡	177±1.29	172±1.35
BVAS >0 — no. (%)§	37 (54)	48 (71)
Prednisolone or prednisone dose — mg/day		
Median	12.0	11.0
Range	7.5–40.0	7.5–50.0
Immunosuppressive therapy at baseline — no. (%)	41 (60)	31 (46)
EGPA diagnostic disease characteristics — no. (%)		
Asthma with eosinophilia	68 (100)	68 (100)
Biopsy evidence¶	25 (37)	31 (46)
Neuropathy‖	32 (47)	24 (35)
Nonfixed pulmonary infiltrates	50 (74)	48 (71)
Sinonasal abnormality	64 (94)	64 (94)
Cardiomyopathy**	13 (19)	7 (10)
Glomerulonephritis	1 (1)	0
Alveolar hemorrhage	3 (4)	1 (1)
Palpable purpura	9 (13)	8 (12)
ANCA-positive status	13 (19)	13 (19)
Relapsing disease — no. (%)	51 (75)	49 (72)
Refractory disease — no. (%)	34 (50)	40 (59)
Duration since diagnosis of EGPA — yr	5.2±4.4	5.9±4.9
Immunosuppressive therapy since diagnosis — no. (%)	56 (82)	49 (72)

MIRRA study

Remission/First relapse



(A) Median prednisolone/prednisone dose (mg/day) during each reported period
(B) LS mean ratio to baseline in blood EOS count



MIRRA study

Approximately half the participants with relapsing or refractory EGPA who were treated with mepolizumab had clinically relevant improvements in the rates of protocol defined remission and relapse, which allowed for reduced CSs use.

Rituximab for the treatment of EGPA

- Patients with EGPA who received RTX as single or repeated courses were identified from four vasculitis centres
- 41 patients (21 women) with EGPA treated with RTX between 2003 and 2013 were identified
- 15 (37%) had refractory, 21 (51%) relapsing and 5 (12%) new onset disease
- 19 received a single course and 22 received repeat-dose rituximab to prevent relapse.

ARD 2014

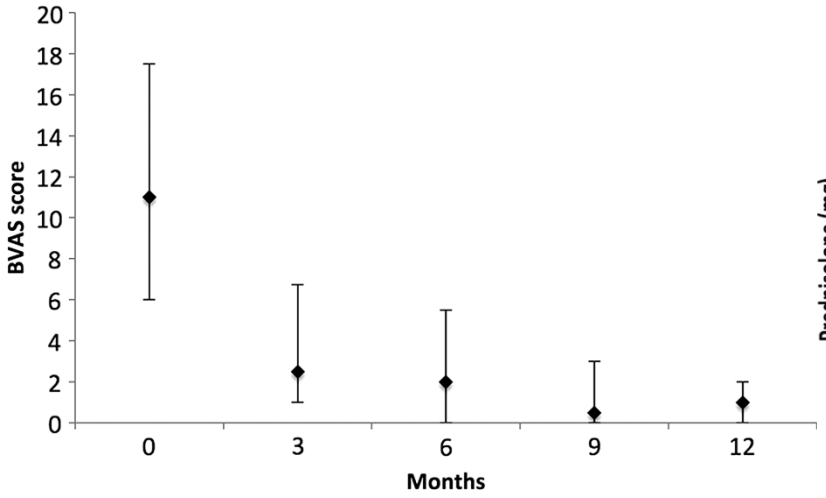
Rituximab for the treatment of EGPA

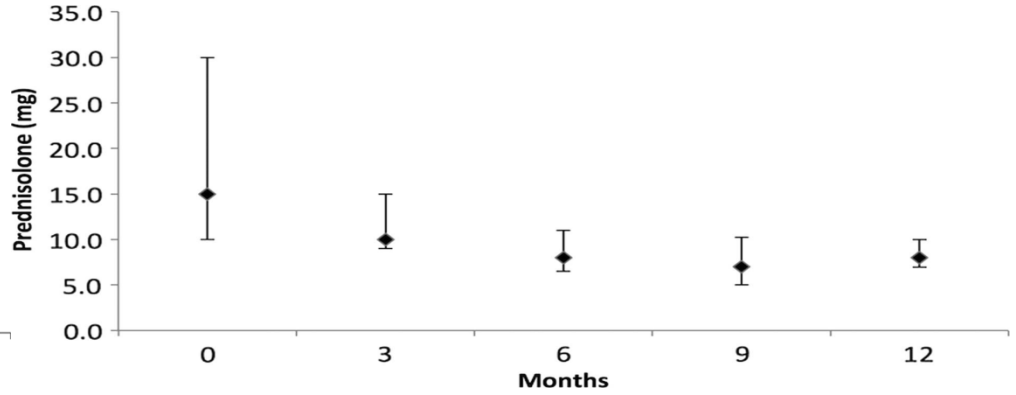
Table 1 Baseline demographics and clinical characteristics of 41 patients with eosinophilic granulomatosis with polyangiitis treated with rituximab

Sex F/M	21/20
Age at first rituximab, years, median (IQR)	54 (38.5–61)
Prior disease duration, months, median (IQR)	46 (11–95.5)
ANCA, number of patients (%)	
Positive (including IF)	18 (44)
Negative	23 (56)
Positive C- or P-ANCA (only IF)*	5 (12)
PR3-ANCA	4 (10)
MPO-ANCA	9 (22)
Biopsy-proven disease	28 (68)
Number of prior immunosuppressive therapies, median (IQR)	2 (1–3)
Immunosuppressive drugs prior to rituximab, number of patients (%)	
Cyclophosphamide	27 (66)
Cumulative cyclophosphamide dose, grams, median (IQR)	12 (8.7–32.5)
Azathioprine	21 (51)
Mycophenolate mofetil	20 (49)
Methotrexate	11 (27)
Intravenous immunoglobulin	7 (17)
Leflunomide	3 (7)
Alemtuzumab	2 (5)
Etanercept	2 (5)
Infliximab	2 (5)
Mepolizumab	1 (2)
Omalizumab	1 (2)
DEI score, median (IQR) at first rituximab treatment	8 (8–10)
BVAS median (IQR) at first rituximab treatment	11 (6–17.5)
Organ involvement according to DEI, number of patients (%)	
Lung (including asthma)	40 (98)
Ear, nose and throat	35 (85)
Arthralgia/arthritis	22 (54)
Skin	20 (49)
Peripheral nervous system	12 (29)
Renal	10 (24)
Gastrointestinal tract	9 (22)
Heart	9 (22)
Eyes	5 (12)
Central nervous system	1 (2)

ARD 2014

Rituximab for the treatment of EGPA





• By 6 months, 83% improved with remission in 34% and partial response in 49%, and by 12 months 49% were in remission and 39% had a partial response.

• **Patients with positive ANCA testing were more likely to achieve remission**: 12/15 (80%) patients who were ANCA+ achieved remission at 12 months compared with 8/21 (38%) who were ANCA- (p=0.013).

Rituximab for the treatment of EGPA

Table 3 Adverse events within 1 year of first rituximab treatment in patients with eosinophilic granulomatosis with polyangiitis

Adverse events	Number of events
All adverse events (any adverse event)	31
Allergic reactions	
Mild urticaria/skin rash	8
Severe reaction (one with worsening of asthma)	2
Infections	
Mild	9
Severe (necessitating hospitalisation)*	6
Chest	3
URTI	2
Pyelonephritis	1

ARD 2014

Rituximab for the treatment of EGPA

RTX is a safe and important alternative to standard therapy in EGPA, both for refractory and relapsing diseases, especially for ANCA+ patients, and also for newly diagnosed patients in whom traditional cytotoxic drugs are contraindicated or undesirable.

Despite the good response rate in this study, complete withdrawal of CSs was generally not feasible

Long-term outcome of the use of rituximab in EGPA and its role as maintenance treatment need to be addressed in future studies.

Anti-IgE

- IgE could be responsible for the degranulation of IgE receptor–bearing cells (e.g., eosinophils, basophils, and mast cells).
- Omalizumab is a recombinant humanized monoclonal antibody targeting the high affinity receptor binding site on IgE.
- The binding of omalizumab to free IgE prevents its interaction with both high-affinity and low-affinity receptors found on the surface of mast cells, basophils, eosinophils, and B cells.
- Omalizumab also induces eosinophil apoptosis and down-regulates the production of inflammatory cytokines, thus exhibiting antiallergic and antiinflammatory properties
- Omalizumab has proven efficacy for the treatment of allergic asthma and allergic rhinitis, with a favorable safety profile.

Anti-IgE Monoclonal Antibody (Omalizumab, Xolair) in Refractory and Relapsing EGPA

- Response was defined as the absence of asthma and/or sinonasal exacerbations with a prednisone dosage of < 7.5 mg/day (complete response) or >7.5 mg/day (partial response).

- 17 patients (median age 45 years) received omalizumab for severe steroid dependent asthma (88%) and/or sinonasal involvement (18%).

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Omalizumab in Refractory and Relapsing EGPA

Table 2. Characteristics associated with disease flares requiring initiation of omalizumab*

Indications for initiation of omalizumab	
Severe steroid-dependent asthma	15 (88)
Severe ENT involvement	3 (18)
High-dose steroid dependency	16 (94)
Pruritus	1 (6)
Active clinical manifestations	
Asthma	17 (100)
No. of exacerbations, median (range)	1 (0–15)
ENT involvement	8 (47)
Non-fixed pulmonary infiltrates	2 (12)
Constitutional symptoms	2 (12)
Arthralgia or arthritis	2 (12)
Cutaneous involvement	2 (12)
Peripheral nervous system involvement	0
Cardiac involvement	0
Renal involvement	0
Laboratory findings	
Eosinophil count, median (range) mm^3	743 (0–2,230)
Serum IgE, median (range) IU/ml	597 (22–3,527)
ANCA positivity	1 (6)
C-reactive protein, median (range) mg/ml	9 (1–64)

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Omalizumab in Refractory and Relapsing EGPA

- After a median follow-up of 22 months, 6 patients (35%) achieved a complete response, 5 patients (30%) achieved a partial response, and 6 patients (35%) had no improvement

- The median prednisone dosage decreased from 16 mg/day at baseline to 11 mg/day at 6 months and 9 mg/day at 12 months.

- Omalizumab was discontinued in 8 patients (47%) during follow-up, because of remission (12.5%), adverse event despite disease remission (12.5%), refractory disease (25%), or relapse (50%). Relapses included retrobulbar optic neuritis attributable to EGPA in 2 patients and severe asthma flare in 2 others.

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Omalizumab in Refractory and Relapsing EGPA

Conclusion

The results of this study suggest that omalizumab may have a corticosteroid-sparing effect in EGPA patients with asthmatic and/or sinonasal manifestations, but reducing the corticosteroid dose may also increase the risk of severe EGPA flares, which raises the question of the safety of omalizumab in patients with EGPA.

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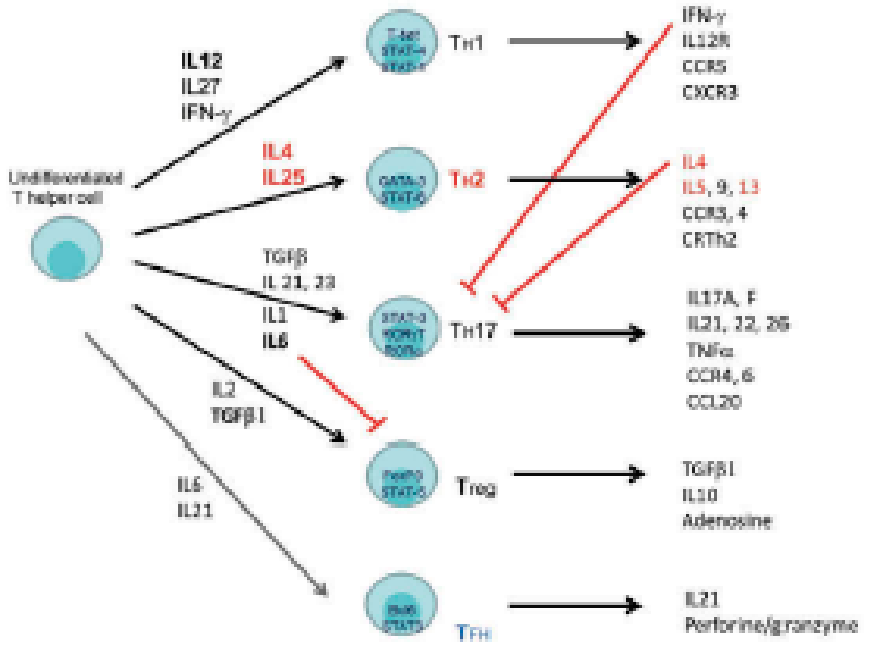
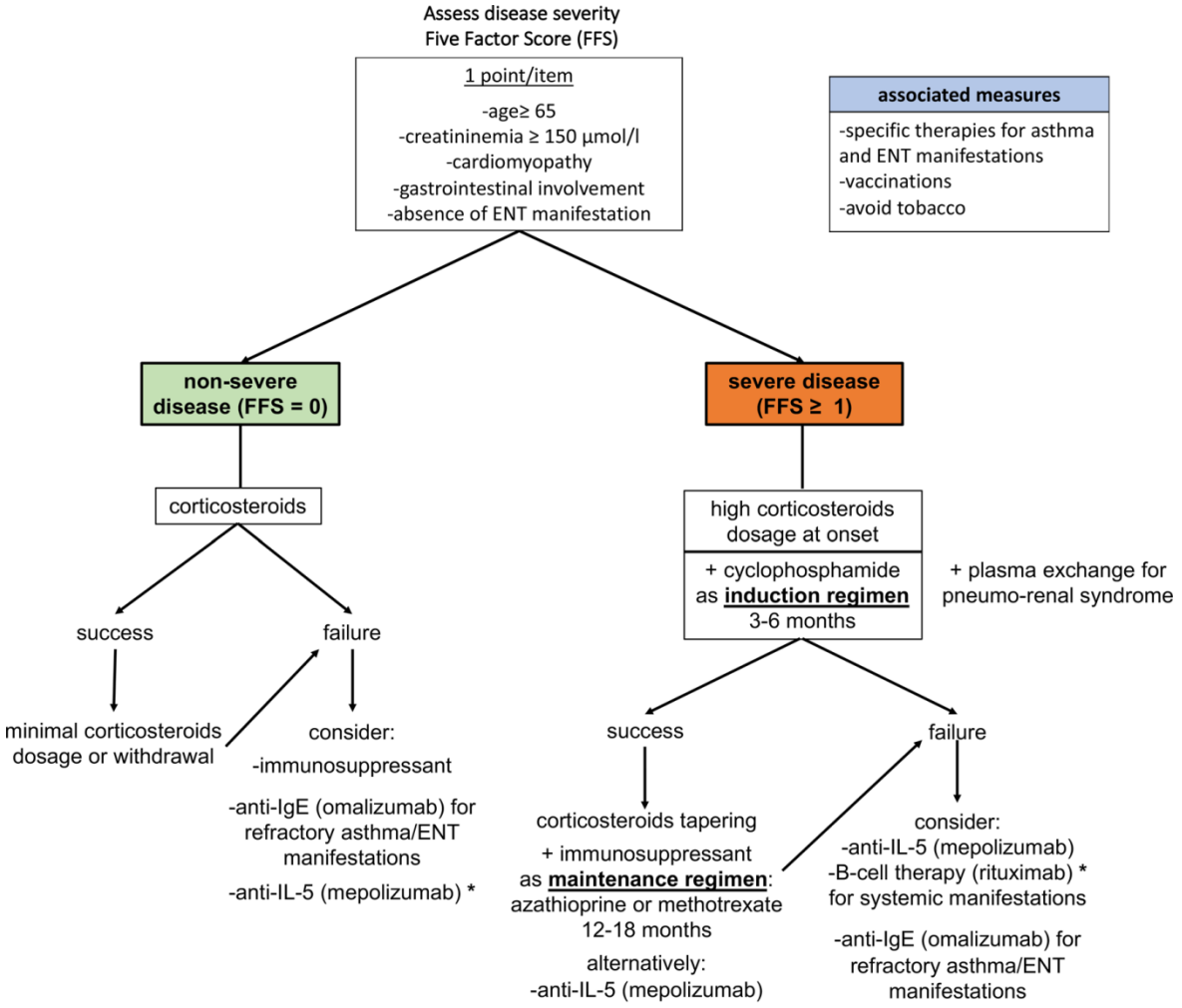
Treatment options of potential interest and/or being under investigation for EGPA

- **Anti-IL2Rα** (CD25 activated T): daclizumab (IgG1)
- **Anti-IL4**
  - nebulized IL4R alfakincept
  - pasolizumab
  - pitakinra (anti-IL4Rα, IL4/IL13)
  - dupilumab (anti-IL4Rα, IL4/IL13)
- **Anti-IL5**
  - ***mepolizumab*** (IgG1)
  - resilizumab (IgG4)
- **Anti-IL5 receptor**
  - benralizumab (IgG1 anti-IL5Ra)
  - (TP1) ASM8 (antisense oligonucleotide βc)
- **Anti-IL9**
- **Anti-IL12/23** ustekinumab
- **Anti-IL13**
  - lebrikizumab (IgG4)
  - tralokinumab (IgG4)
- **Anti-IL17**: ixekizumab
- **Anti-IL25**

- **Anti-neutrophils**, anti-IL8/CXCR2
- **Low-dose IL2** (to increase Tregs)



Main therapeutics and treatment algorithm in EGPA



* Targeted biologic therapies currently under evaluation in clinical trials

Ευχαριστώ πολύ για την προσοχή σας