대 한 류 마 티 스 학 회 지
Vol. 17, No. 2, June, 2010
DOI:10.4078/jkra.2010.17.2.108

□ 종 설 □

엄 완 식

= Abstract =

ANCA Associated Vasculitis

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Primary antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) constitute a group of small vessel vasculitides that includes Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome. Recently, many in vitro and in vivo studies have highlighted the role of ANCA as the main pathophysiological factor in the development of AAV. Two remarkable studies on ANCA pathogenesis were recently reported. One study examined anti-lysosomal membrane protein-2, which supports the 'shared epitope' theory. The other examined the neutrophil extracellular trap that is released by neutrophils primed by ANCA. Each disease of AAV shows a broad spectrum of the clinical features and severities, which makes it difficult to diagnose and treat them. Considerable effort has been made in the past decades to improve the treatment outcomes, reduce the incidence of relapse and avoid drug toxicity. This review describes the current understanding of AAV along with a few Korean reports.

Key Words: ANCA associated vasculitis, Small vessel vasculitis, Wegener's granulomatosis, Microscopic polyangiitis, Churg-Strauss syndrome

＜접수일 : 2010년 6월 3일, 수정일 : 2010년 6월 5일, 심사통과일 : 2010년 6월 7일＞

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서 론

(antineutrophil cytoplasmic antibody associated vasculitis, ANCA) (small vessel vasculitis) (ANCA) (Wegener's granulomatosis), (microscopic polyangiitis, MPA), - (Churg-Strauss syndrome), (renal limited vasculitis) .

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ANCA ANCA , .

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1866 Kussmaul Maier (polyarteritis nodosa, PAN) (1) 70 1931 Klinger (atypical PAN) (2). 1932 Wegener 3 (3).

, , (glomerulonephritis, GN) .

(pauci-immune GN) .

‘ ’ (‘microscopic’ form of PAN) 1923 Wohlwill (focal segmental necrotizing GN) (4).

(5,6).

1990 (American College of Rheumatology, ACR) (7) 1994 Chapel Hill Consensus Conference (CHCC) (8). CHCC (hypersensitivity vasculitis) (5,9) .

1990 .

- 1951 Churg Strauss , , “allergic granulomatous and angiitis” (10). - , ANCA ANCA . ANCA .

ANCA .

역 학

ANCA . ANCA CHCC ACR ACR CHCC

Table 1. Summary of prevalence, incidence and onset age for ANCA associated vasculitis

	Prevalence (/million)	Incidence (/million/year)	Onset age
Wegner's granulomatosis	24～160 (11-15)	3～11 (15, 20-22)	51～66 (11, 13-15)
Microscopic polyangiitis	25～94 (12-15)	2～8 (15, 20-24)	60～71 (11, 13-15)
Churg-Strauss syndrome	11～14 (11, 23, 25)	2～7 (23, 26)	50～61 (11, 13)

, , ANCA
(ANCA-negative undifferentiated small vessel vasculitis) .

0 24C 4 (1O 16 //

87 (20.4%), 337 (79.1%), - 2 (0.5%) 4 (31). 61% MPO-ANCA . MPO-ANCA PR3-ANCA (32). ANCA - MPO-ANCA PR3-ANCA . . ANCA , ANCA , .

국내 연구현황

ANCA . ANCA KoreaMed (http://www.koreamed.org) . ‘Wegener’s granulomatosis’, ‘polyarteritis nodosa’, ‘microscopic polyangiitis’, ‘Churg-Strauss syndrome’, ‘vasculitis’ . PubMed (http://www.ncbi.nlm.nih.gov/pubmed) ‘Korean’ . (systemic review) . 1959 (33) 50 . 2001 10 1990 ACR 5 (limited form) 6 ANCA (cytoplasmic ANCA, c-ANCA) ANCA ANCA (perinuclear ANCA, p-ANCA) (34). 10 8 (oral cyclophosphamide, Cyc+glucocorticoid, GC) 2 methotrexate (MTX)+GC . 70% 1 1 Cyc+GC *Pneumocystis carinnii* . (30% vs 44%), (40% vs 15%) (50% vs 13%) . 1999 (35) 20 . - , . 2009 18 CHCC 18 (36). , . ANCA 94% p-ANCA . ANCA c-ANCA . 1990 ACR 89% B (endemic area) anti-HBs 50% . 17 Cyc+GC 1 GC . 56% (diffuse alveolar hemorrhage) . 1991 (37-40) 60 . 2006 14 ACR 27 (41). CHCC . . - 1989

(42) 60
. 2006 10
ACR 17
(43).
13～50%
0% ANCA
35～77% 5.9% .
94%
29% 1 (5.9%) .
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European Vasculitis Study (EUVAS) Group, International Network for the Study of Systemic Vasculitis, French Vasculitis Study Group, Vasculitis Clinical Research Consortium (VCRC)
(44). Research Group of Intractable Vasculitis
(45).

병 인

1. 유전적 위험요인

ANCA

(46)
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ANCA
ANCA
‘ ’ .
(genome wide association study)
ANCA
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(candidate gene study)

α-1-antitrypsin (A1AT, odd ratio, OR 3.0～9.4) Z (null)
(47). α-1-antitrypsin PR3
Z α-1-antitrypsin
PR3 PR3
.
HLA-DPB1*0401 (OR 3.0) (48), CD226 (OR 1.2～1.4) (49), FCGR3B (copy number variation) (OR 2.46) (50) . -
HLA-DRB4 (OR 1.9～2.5) (51,52), HLA-DRB3 (OR 0.54～0.61) (51,52) .

CD226
- (49)
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2. 환경적 위험요인

ANCA
.
(silica)

OR 2~14 -
(53,54). ,
(55) .

(56). prophylthiouracil
hydralazine MPO-ANCA (2).
(57), ANCA
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질환분류 및 정의

(European League Against Rheumatism, EULAR)
(58).
ACR CHCC
ANCA 1990 ACR (7) (59-61)
1994 CHCC (8) . - Lanham (Hammer-
ACR smith) (62).

. CHCC

Table 2. ACR classification criteria and CHCC nomenclature of ANCA associated vasculitis

	ACR criteria (1990) (63)	CHCC Nomenclature (1994) (8)
Wegner's granulomatosis	1. Nasal or oral inflammation 2. Chest X-ray showing nodules, infiltrates (fixed) or cavities 3. Microscopic hematuria or red cell casts in urine 4. Granulomatous inflammation on biopsy Two criteria classify WG with a sensitivity of 88.2% and specificity of 92.0%	· Granulomatous inflammation involving the upper and lower respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels · Necrotizing GN is common
Microscopic polyangiitis		· Necrotizing vasculitis, with few or no immune deposits, affecting small vessels · Necrotizing arteritis of small and medium-sized arteries may be present. Necrotizing GN is common. Pulmonary capillaritis often occurs.
Churg-Strauss syndrome	1. Asthma 2. Eosinophilia 3. Neuropathy 4. Pulmonary infiltrates (non-fixed) 5. Sinusitis 6. Positive biopsy Four criteria classify CSS with a sensitivity of 85% and specificity of 99.7%	· Eosinophil-rich, granulmatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma and eosinophilia

ACR: American College of Rheumatology, CHCC: Chapel Hill Consensus Conference, WG: Wegner's granulomatosis, GN: glomerulonephritis, CSS: Churg-Strauss syndrome

병태생리

ANCA 1982 (64) *in vitro* *in vivo* ANCA . ANCA PR3 MPO . ANCA ANCA , , , (65-68). B rituximab B ANCA (69).

in vitro ANCA , (tumor necrosis factor-α, TNF-α) IL-8 (interleukin-8), TGF-β (transforming growth factor-β)

(primary granules) PR3 MPO (70-72).

PR3 (73) PR3 (74). 1990 Falk IgG-ANCA TNF-α superoxide radical (hydrogen peroxide) (respiratory burst) (75). ANCA

(adhesion) (76).

in vitro ANCA , , ANCA ANCA (1) (77,78).

ANCA *in vivo* 2002 Xiao (human-like vasculitis) (79). MPO (knock out) MPO MPO . MPO B T Rag(-/-) MPO-ANCA . MPO-ANCA Rag(-/-) .

MPO-ANCA .

PR3 MPO-ANCA PR3-ANCA .

Kain lysosomal membrane protein-2 (LAMP-2) ANCA (80). anti-human LAMP-2 FimH 100% ‘ (molecular mimicry)’ . , FimH LAMP-2 ANCA . anti-LAMP MRL/lpr (81) ANCA .

(neutrophil extracellular trap, NET) ANCA (82).

NET NET (83). ANCA NET . ANCA NET NET PR3 MPO . *In vitro* ANCA NET

(89).
(effector memory) CD4+T
(90-92).
B CD20 rituximab
ANCA
B
ANCA B
(93). ANCA
B B
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임상양상

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(94).
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ENT .
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ANCA
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(hyperplastic gingivitis) (95).
ANCA
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(96).
(splinter hemorrhage), (livedo reticularis),
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(leukocytoclastic vasculitis)
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ANCA
‘red eye’ . ‘red eye’
ANCA
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Table 3. Clinical manifestations of ANCA associated vasculitis

	WG (100,101)	MPA (102)	CSS (62,103-106)
ANCA positivity	80～95%	70%	50%
ANCA antigen	PR3: 70～80%	PR3: 15～30%	PR3: 15～20%
Specificity* (107)	MPO: 10～15%	MPO: 50～70%	MPO: 30～40%
Fundamental histology	Leukocytoclastic vasculitis; necrotizing granulomatous inflammation (rarely seen in renal biopsy specimen)	Leukocytoclastic vasculitis; no granulomatous inflammation	Eosinophilic tissue infiltrates and vasculitis: granulomas have eosinophilic necrosis
ENT	79～94%	11%	50～60%
	Nasal septal perforation, saddle-nose deformity, sinusitis, conductive or sensorineural hearing loss, subglottic stenosis	Absent or mild	Nasal polyps, allergic rhinitis, sinusitis, conductive hearing loss
Eye	29～65%	＜5%	＜5%
	Orbital pseudotumor, scleritis (risk of scleromalacia perforans), episcleritis, uveitis	Occasional eye disease, scleritis, episcleritis, uveitis	Occasional eye disease, scleritis, episcleritis, uveitis
Lung	53～83%	25%	90～100%
	Nodules, infiltrates or cavitary lesions; alveolar hemorrhage	Alveolar hemorrhage	Asthma, fleeting infiltrates, alveolar hemorrhage
Kidney	23～77%	79%	25～58%
	Segmental necrotizing GN, rare granulomatous features	Segmental necrotizing GN	Segmental necrotizing GN
Heart	13%	＜5%	8～47%
	Occasional valvular lesions	Rare	Heart failure
Peripheral nerve	20%	58%	66～76%
	Vasculitic neuropathy	Vasculitic neuropathy	Vasculitic neuropathy
Eosinophilia			90～100%
	Mild eosinophilia occasionally	None	All

*These percentages come from studies of Europe and the United States

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(rapidly progressive GN) .

ANCA

. ANCA (mononeuritis multiplex)

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(red cell cast) ANCA .

(transverse myelitis)

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ANCA

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(ileum) . .

(98,99). ANCA

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ANCA , ANCA

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(97). ANCA

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(16). -

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, (45) .

α-1-antitrypsin

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- ANCA ANCA

Table 4. Mimics and secondary causes of vasculitis (108)

Mimics of vasculitis	Secondary causes of vasculitis	
Atheroembolic disease	Infections	Tuberculosis
Atheromatous vascular disease		Hepatitis B
Anti-phospholipid syndrome		Hepatitis C
Multiple myeloma		HIV
Infective endocarditis		Parvovirus
Other chronic infections		Cystic fibrosis
Para-neoplastic syndromes		
Genetic vascular disorders (e.g. Marfan's syndrome)	Malignancy	Lymphoma
Autoinflammatory syndromes		Solid organ malignancy
Hypersensitivity reactions	Connective tissue disorders	Rheumatoid arthritis
Cocaine and amphetamine abuse		Systemic lupus erythematosus
		Scleroderma
		Sjögren's syndrome
	Drugs	Penicillamine
		Propylthiouracil
		Hydralazine
		Minocycline
		Cocaine
	Environmental exposure	Dusts
		Silica

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ACR CHCC .

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ANCA

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(secondary)

(4).

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(108). ANCA

ANCA

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ANCA ANCA

c-ANCA, p-ANCA

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ANCA

(109,110). ANCA

ANCA ANCA

(97).

ANCA 1/3

(111).

ANCA

ANCA .

(ESR) , C (CRP)

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질환 활성도, 장기침범, 손상의 측정

ANCA

Birmingham Vasculitis Activity Score (BVAS) (112) BVAS/WG

(113).

BVAS

ELK (114) Disease Extent Index (DEI)

(115).

physician global assessment BVAS (112,113).

(Vasculaitis Damage Index, VDI)

(116).

Short Form Questionnaire 36 (SF-36) (44).

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1996 Five Factor Score (FFS) (117) 2001

(118). FFS

① 1 g ② >140 μmol/L (1.58 mg/dL) ③ ④ ⑤ .

ANCA

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. 2007

ANCA

(155) ANCA
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ANCA
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(5, 6).

1. 관해유도(Remission induction)

1) 국소 또는 조기 전신 질환(Localized or early systemic disease)

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(< 120 μmol/L, 1.4 mg/ dL)
.
Cyc MTX (101, 120,123,157-161).

Table 5. Definitions for disease stages of ANCA associated vasculitis according to EULAR

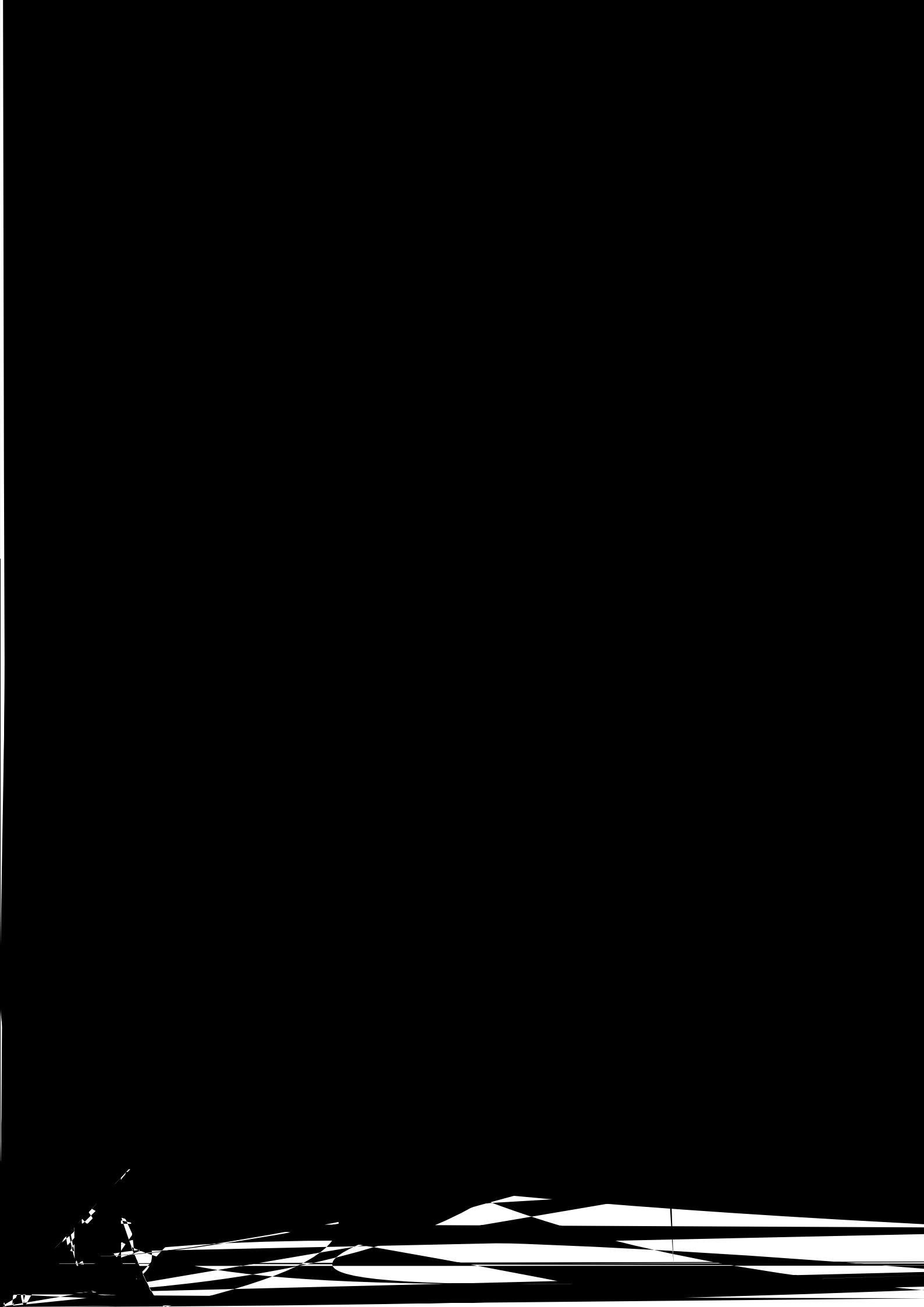
Clinical subgroup	Systemic vasculitis outside ENT tract and lung	Threatened vital organ function	Other definitions	Serum creatinine (μmol/L)	Reference
Localized	No	No	No constitutional symptoms, ANCA typically negative	< 120 (1.4 mg/dL)	
Early systemic	Yes	Yes	Constitutional symptoms present, ANCA-positive or -negative	< 120	
Generalized	Yes	Yes	ANCA-positive	< 500 (5.6 mg/dL)	Jayne et al (128)
Severe	Yes	Organ failure	ANCA-positive	> 500	Jayne (156)
Refractory	Yes	Yes	Refractory to standard therapy	Any	Jayne (156)

ANCA: anti-neutrophil cytoplasmic antibody, ENT: ear, nose and throat

Table 6. Recommendation for use and definition of activity states in vasculitis (155)

Activity state	Definition
Remission	Absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy. The term “active disease” is not restricted to vasculitis only, but also includes other inflammatory features like granulomatous inflammation in WG or tissue eosinophilia in CSS.
Response	50% reduction of disease activity score and absence of new manifestations
Relapse	Re-occurrence or new onset of disease attributable to active vasculitis
Major	Re-occurrence or new onset of potentially organ- or life-threatening disease
Minor	Re-occurrence or new onset of disease which is neither potentially organ- nor life-threatening
Refractory disease	Unchanged or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy in acute AAV, or Lack of response, defined as ≤50% reduction in the disease activity score, after 6 weeks of treatment, or Chronic, persistent disease defined as presence of at least one major or three minor items on the disease activity score list (eg, BVAS or BVAS/WG) after ≥12 weeks of treatment
Low-activity disease state	Persistence of minor symptoms (eg, arthalgia, myalgia) that respond to a modest increase of the GC dose and do not warrant an escalation of therapy beyond a modest dose increase inthe current medication

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis, BVAS: Birmingham Vasculitis Activity Score, BVAS/WG: Birmingham Vasculitis Activity Score for Wegener’s granulomatosis, CSS: Chrug-Strauss syndrome, GC: glucocorticoid, WG: Wegener’s granulomatosis



GC 10 mg/day 6～18 (128).

2. 관해유지(Remission maintenance)

ANCA Cyc . azathioprine (2 mg/kg/day) (128,169), MTX (20～25 mg/kg/week) (134,170), leflunomide (20～30 mg/day) (171) 18 24 (128,172) . Mycophenolate mofetil (173-175).

3. 불응 또는 재발질환(Refractory or relapse disease)

ANCA . (176,177). mycophenolate mofetil (173,178), anti-thymocyte globulin (179), infliximab (180), rituximab (69,181-184) (8). etanercept (136).

Table 7. Dose modification of pulsed cyclophosphamide as used in a randomisedcontrolled trial comparing the efficacy of daily oral versus pulsed cyclophosphamide for renal vasculitis (http://www.vasculitis.org/protocols/CYCLOPS.pdf)

Pulsed CYC dose reductions for renal function and age		
Age, years	Creatinine (μmol/litre)	
	＜300 (3.4 mg/dL)	300～500 (3.4～5.6 mg/dL)
＜60	15 mg/kg/pulse	12.5 mg/kg/pulse
60～70	12.5 mg/kg/pulse	10 mg/kg/pulse
＞70	10 mg/kg/pulse	7.5 mg/kg/pulse

The trial did not include a separate regimen for patients with a creatinine of ＜150 μmol/litre (1.7 mg/dL). CYC: cyclophosphamide

Table 8. Alternative remission induction treatments in relapsing, refractory or persistent disease (155)

Drug	Dose	Reference
Intravenous immunoglobulin	2 g/kg over 5 days	Muso et al, Jayne et al (176,177)
15-Deoxyspergualin	0.5 mg/kg/day till white cell count nadir of 3,000/μL, then wait until the white cell count returns to ≥4,000/μL and repeat the dose for six cycles	Burke et al (185)
Anti-thymocyte globulin	2.5 mg/kg/day for 10 days adjusted according to lymphocyte count: no anti-thymocyte globulin if ＜150/μL, 1.5 mg/kg/day if 150～300/μL, full dose if ＞300/μL	Schmitt et al (179)
Infliximab	3～5 mg/kg/infusion every 1 to 2 months	Booth et al (180)
Mycophenolate mofetil	2 g/day	Koukoulaki et al, Stassen et al (173,178)
Rituximab	375 mg/m^2 body surface area weekly for 4 weeks	Keogh et al, Keogh et al, Stasi et al, Brihaye et al, Eriksson et al (69,181-184)

ANCA rituximab
6 91% (69,
181-184) .

결 론

ANCA
10～20
60～70 .

MPO-ANCA
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ANCA ANCA

LAMP-2 ANCA
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NET
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ANCA
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Cyc GC
Cyc
Cyc MTX .
18
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ANCA

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