# 臨床 総論　3. RCT (MPA/GPA)

- Review (Management of AAV)：2020 BMJ
- Avacopan：2021 NEJM

# Management of ANCA associated vasculitis

CLINICAL REVIEW

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[BMJ 2020;368:m421]
[doi: 10.1136/bmj.m421]

- Guidelineには最近のStudyが含まれない：BSR(2014), EULAR(2015)

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- IVCYの用量調整：　**CYCLOPS**(2009)
- 寛解導入 RTX vs IVCY：　**RAVE**(2010, 2013), **RITUXIVAS**(2010)
- 寛解導入 MTX, MMF：　**NORAM**(2005), **MYCYC**(2019)
- 血漿交換：　**MEPEX**(2007), **PEXIVAS**(2020)
- 維持療法 経口：　**CYCAZAREM**(2003), **WEGENT**(2008), **IMPROVE**(2010)
- 維持療法 RTX：　**MAINRITSAN1**(2014), **MAINRITSAN2**(2018), **RITAZAREM**(2019)
- 治療の中止：　**REMAIN**(2017)

寛解導入
poCY vs IVCY

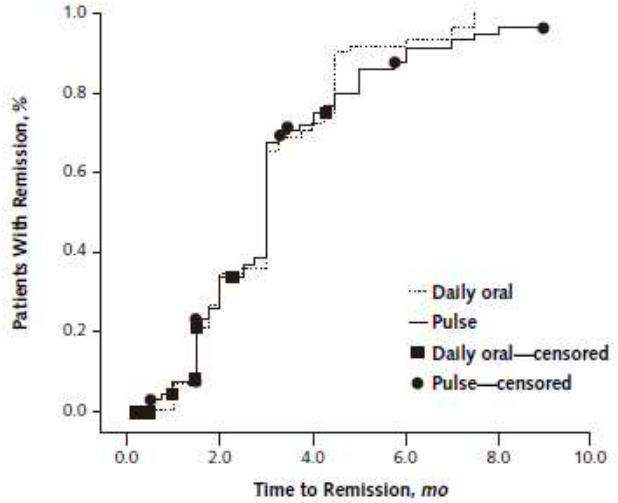
# CYCLOPS (2009)

[Ann Intern Med. 2009;150:670-680.]

## Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

### A Randomized Trial

Kirsten de Groot, MD; Lorraine Harper, MD, PhD; David R.W. Jayne, MD, PhD; Luis Felipe Flores Suarez, MD, PhD; Gina Gregorini, MD; Wolfgang L. Gross, MD; Rashid Luqmani, MD; Charles D. Pusey, MD, PhD; Niels Rasmussen, MD; Renato A. Sinico, MD; Vladimir Tesar, MD, PhD; Philippe Vanhille, MD; Kerstin Westman, MD, PhD; and Caroline O.S. Savage, MD, PhD, for the EUVAS (European Vasculitis Study Group)




| | | | | | |
|---|---|---|---|---|---|
| Daily oral | 73 | 43 | 18 | 4 | 0 |
| Pulse | 76 | 46 | 15 | 4 | 2 |

| time from entry (weeks) | prednisolone dosage[1] (mg/kg/day) | prednisolone dosage (mg/day for 60 kg) |
|---|---|---|
| 0 | 1 | 60 |
| 1 | 0.75 | 45 |
| 2 | 0.5 | 30 |
| 3 | 0.4 | 25 |
| 6 | 0.33 | 20 |
| 8 | 0.25 | 15 |
| | prednisolone dosage (mg/day) | |
| reduce at end of month 3 | 12.5 | 12.5 |
| reduce at end of month 5 | 10 | 10 |
| during months 12 - 15 | 7.5 | 7.5 |
| during months 15 - 18 | 5 | 5 |

PSLは1wから減量, 5Mで10mg, 1Yで7.5mg, 15Mで5mg

- Open-label, multicenter, RCT(18M観察)
- poCYとIVCYの寛解導入の比較：IVCYレジュメの基礎
- 新規診断 generalized AAV [腎炎あるがlife-threating ではない]を対象に下記寛解導入, 寛解+3M治療(max 12M). 維持はどちらもAZA 2mg/kg
- IVCY群(76人):15mg/kg/2-3w(x10)+PSL
- poCY群(73人): 2mg/kg, 寛解後3M 1.5mg/kg+ PSL
- Primary endpoint：寛解までの時間
- 結果: 両群の寛解までの時間, 9か月時点での寛解患者比は同等. 積算IVCY 8.2g, 積算poCY 15.9gと有意差あり(p<0.001). IVCYはleukopeniaが有意に少ない.
- 結論：IVCYはpoCYと同等の寛解率で, 積算量は有意に少なく, leukopeniaも少ない.

# CYCLOPS; IVCY protocol

| Time (weeks)[1] | pulse no.[2] |
|---|---|
| 0 | 1 |
| 2 | 2 |
| 4 | 3 |
| 7 | 4 |
| 10 | 5 |
| 13 | 6 |
| 16 | 7 |
| 19 | 8 |
| 22 | 9 |
| 25 | 10 |

**Pulsed CYC dose reductions for renal function and age**

| age (years) | creatinine (umol/l) 150-300 | 300-500 |
|---|---|---|
| < 60 | 15 mg/kg/pulse | 12.5 mg/kg/pulse |
| > 60 and < 70 | 12.5 " " " | 10 " " " |
| > 70 | 10 " " " | 7.5 " " " |

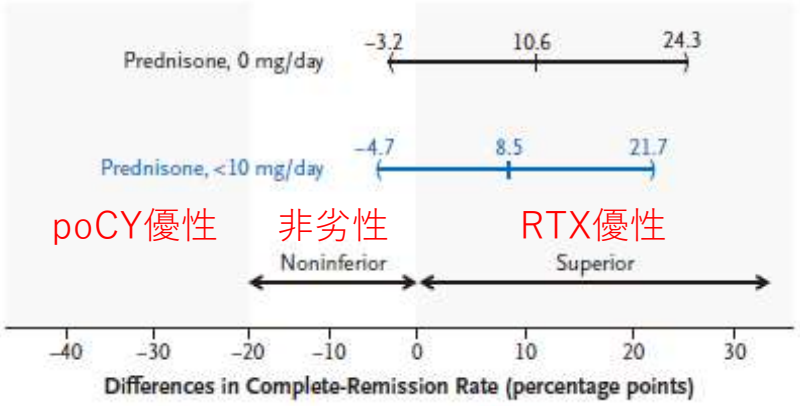
1. Reductions for renal function and age according to table above.
2. Maximum CYC pulse is 1.2g.
3. Dissolve cyclophosphamide in water for injection, then dilute in saline 0.9% 500 ml and administer as I.V. drip over one hour.
4. Mesna is optional and will be administered orally in the same dose in mg as CYC in mg either from I.V. vials or in the form of tablets on days when CYC is administered. (If it has to be administered I.V., reduce mesna dose to 60% of the CYC dose).
5. Prevention of emesis: the choice of antiemetic drugs to cover the CYC pulses should follow local practice. Ondansetron is suitable for this indication.
6. Check FBC on day of pulse or previous day. If WBC prior to pulse < 4 x $10^9$/L, then postpone pulse until WBC > 4 x $10^9$/L, while checking WBC at least weekly. Reduce dose of pulse by 25%. With any further episodes of leucopenia, make equivalent dose reduction .
7. Check FBC between days 10 and 14 after a pulse. If the leucocyte nadir (i.e. the lowest leucocyte count between two CYC pulses) is < 3 x $10^9$/L, even if the WBC just previous to the next pulse is > 4 x $10^9$/L, then reduce the dose of the next pulse by:
   a) leucocyte nadir 1 - 2 x $10^9$/L reduce CYC dose of last pulse by 40 % of previous dose.
   b) leucocyte nadir 2 - 3 x $10^9$/L reduce CYC dose of last pulse by 20 % of previous dose.

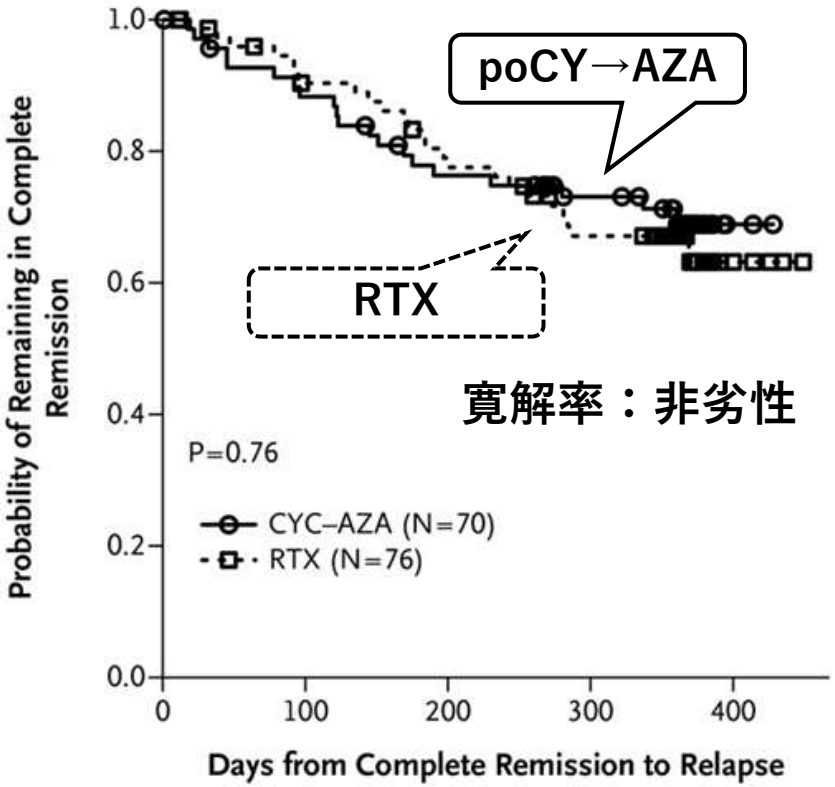
- 15mg/kg, 年齢とCrで減量
- 最大1.2g
- 500mL生食で溶解し1hrで点滴
- MesnaをCY同量内服 or 60% iv
- 制吐剤を使う(Ondansetron)
- 投与前血算確認しWBC < 4,000/μl なら回復まで延期, 25%減量投与.
- Pulse10-14日後のnadirがWBC <3,000/μlなら次回減量.
  - Nadir 1-2,000で40%減量.
  - Nadir 2-3,000で20%減量.

寛解導入
RTX vs poXY

# RAVE (2010, 2013)

[NEJM. 2010;363:221-232., NEJM. 2013;369:417-417.]

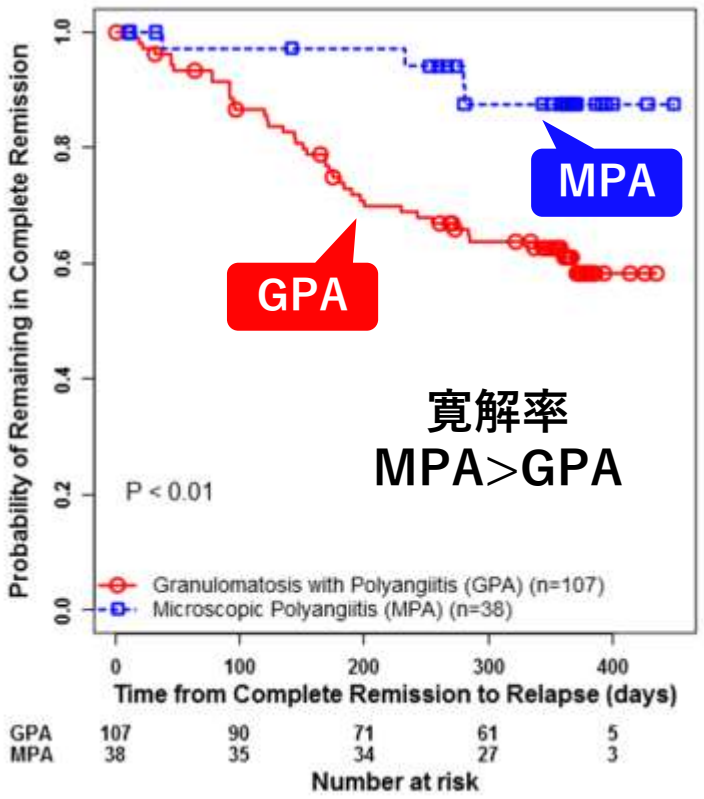


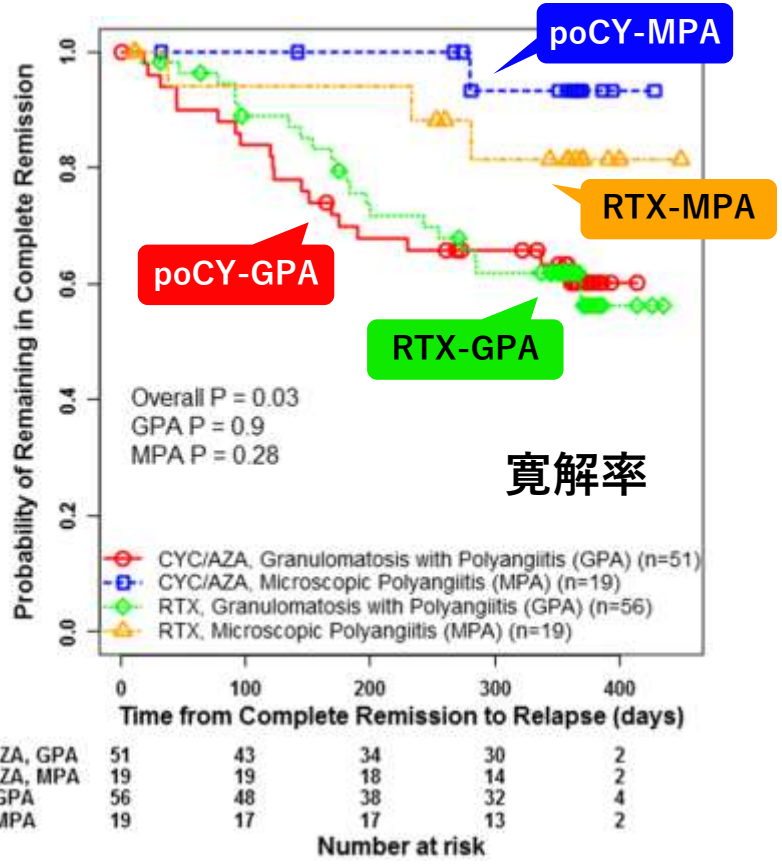

- Open-label, multicenter, RCT(18M観察)
- ANCA⁺, severe GPA/MPA(BVAS/WG≧3)の寛解導入(50%新規/50%再燃例).
- RTX [375mg/m²/w x 4回]vs poCY [2mg/kg]で3-6か月寛解導入→RTX群は維持無, poCY群はAZP 2mg/kg/d.
- GCは1mg/kgで開始, 4wで40mg, 5M以内に0mg
- Primary endpoint：6か月時点[2010]のPSL 0mgのCR率, BVAS/WG 0, 12/18か月まで観察[2013]
- RTX群(99人)：6M CR 64% [非劣性 p<0.001], 18M再燃32% [poCYと有意差なし p=0.76]
- poCY群(98人)：6M CR 53%, 18M 再燃29%
- 有害事象：poCYで肺炎/白血球↓. 死亡は両群とも2名.
- 結論：RTXとpoCYの寛解導入に有意差なし（同等）
- RTXは再燃例のCR率高い(67%vs42%), 腎とDAHに効く

# RAVE(続き)

## MPAとGPAの比較

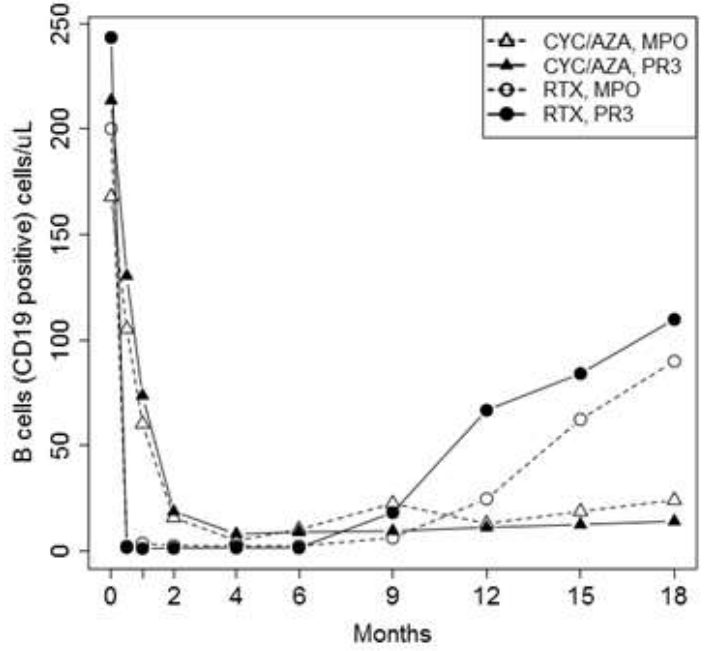



- GPAの寛解率はMPAより有意に低い（p=0.01）




- RTXとpoCY：非劣性
- MPAでもGPAでもいえる

## B細胞除去




- RTX2回でCD19⁺細胞陰性化，6Mまで持続．poCYも持続
- RTX再発例の87.5%，非再発例の66%でCD19⁺検出．再発予測因子ではなかった
- ANCA/CD19⁺細胞ともに陰性の場合は再燃のリスク低い

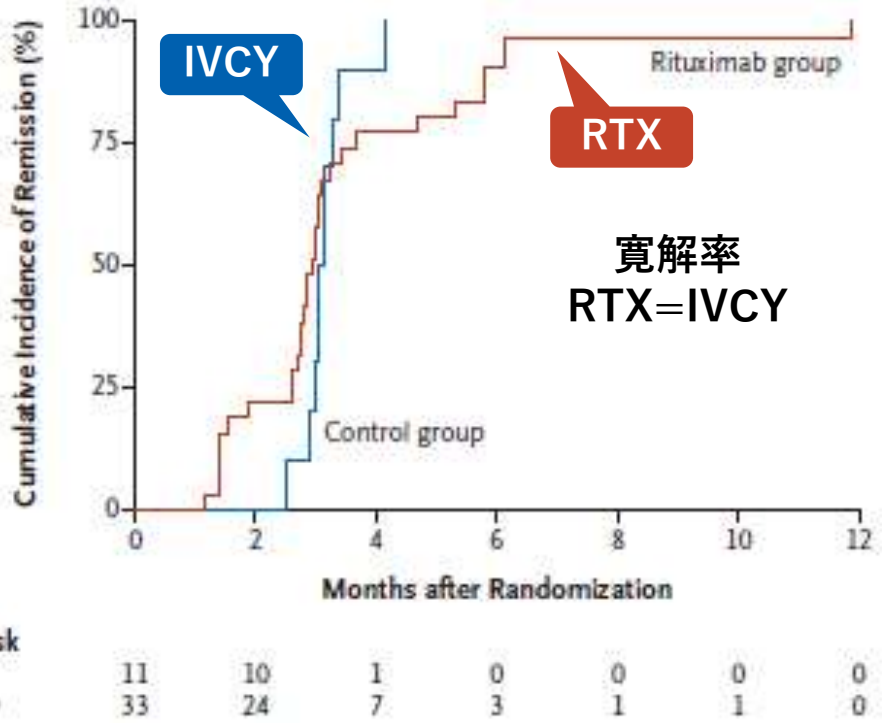
寛解導入
RTX vs IVCY

# RITUXIVAS (2010)

[N Engl J Med 2010;363:211-20.]

## Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, B.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. Jayne, M.D., F.R.C.P., for the European Vasculitis Study Group




| Pulsed CYC dose reductions for renal function and age | | |
|---|---|---|
| age (years) | creatinine (umol/l) <300 | >300 |
| < 60 | 15 mg/kg/pulse | 12.5 mg/kg/pulse |
| > 60 and < 70 | 12.5 " " " | 10 " " " |
| > 70 | 10 " " " | 7.5 " " " |

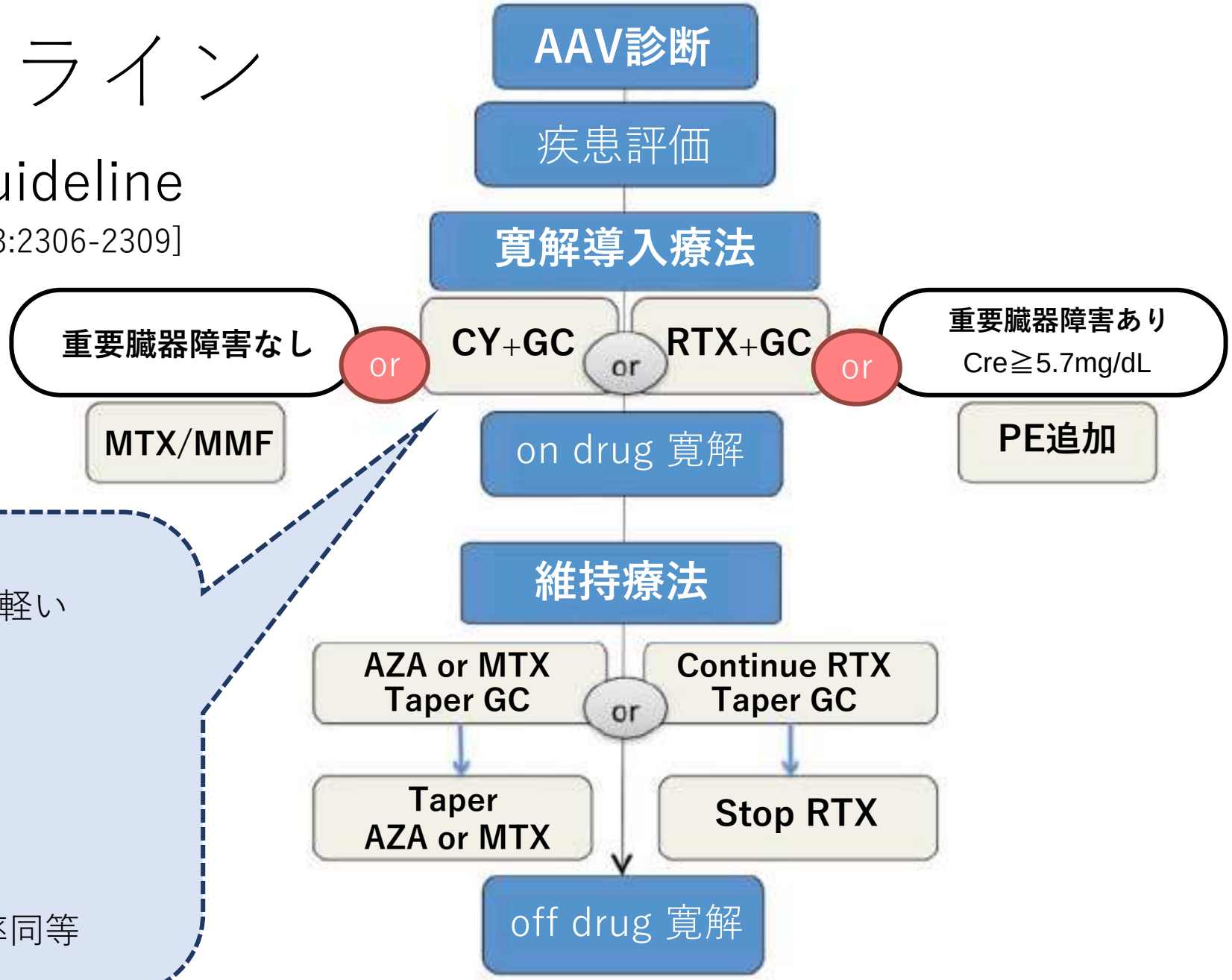
| time from entry (weeks) | prednisolone dose (mg/kg/day) |
|---|---|
| 0 | 1 (max 60mg) |
| 1 | 0.75 |
| 2 | 0.5 |
| 3 | 0.4 |
| 6 | 0.33 |
| 8 | 0.25 |
| | prednisolone dosage (mg/day) |
| reduce at end of month 3 (16 weeks) | 12.5 |
| reduce at end of month 4 (20 weeks) | 10 |
| reduce at end of month 5 (24 weeks) | 7.5 |
| reduce at end of month 6 (28 weeks) | 5 |
| 18- 24 months | Reduce from 5 to 0 |

- Open-label, multicenter, RCT(12M観察)
- ANCA+, 新規発症, 腎炎合併AAVの寛解導入.
- RTX群: 375mg/m$^2$/w x 4回, 1/3回 IVCY, 維持(-)
- IVCY群: 15mg/kg/2-3w x 10回→ AZP 2mg/kg/d
- mPSL 1g pulse→ 1mg/kg→1w減量→6M 5mg
- Primary endpoint: 12Mで寛解6M≧(BVAS 0)
- RTX群(33人)：寛解維持 76% [6M≧],
  寛解までの期間 90d, 再燃15%
- IVCY群(11人)：寛解維持 82% [6M≧],
  寛解までの期間 94d, 再燃11%
- 有害事象：発生時期・頻度ともRTX=IVCY.
- GC量・BVASも両者同じ
- 結論：新規腎炎AAVに対する, RTXとIVCYの寛解導入に有意差なし（同等）

# AAV治療ガイドライン

## 2014 BSR and BHPR guideline

[Rheumatology 2014;53:2306-2309]




**CYCLOPS (2009)**
- IVCY＝poCYと寛解率同等, AE軽い

**RAVE (2010, 2013)**
- RTX=poCYと寛解率非劣性
- Severe GPA/MPAが対象
- GPAは寛解しづらい

**RITUXIVAS(2010)**
- 腎炎AAVでRTX=IVCYと寛解率同等

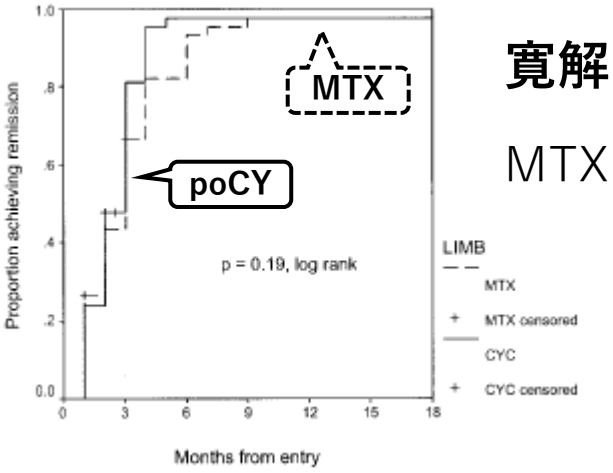
寛解導入
poCY vs MTX

# NORAM (2005)

[Arthritis Rheum. 2005;52(8):2461-9.]

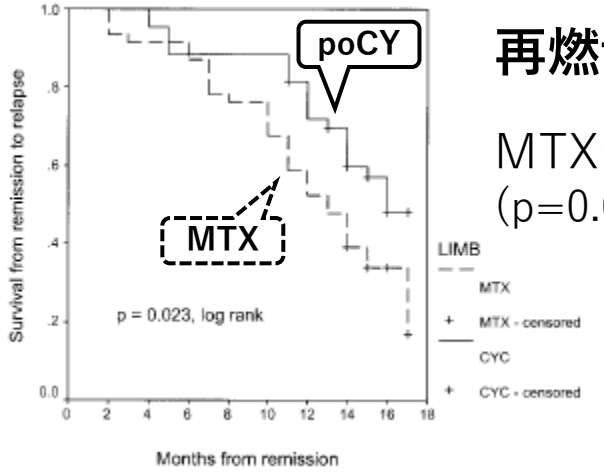
## Randomized Trial of Cyclophosphamide Versus Methotrexate for Induction of Remission in Early Systemic Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Kirsten de Groot,[1] Niels Rasmussen,[2] Paul A. Bacon,[3] Jan Willem Cohen Tervaert,[4] Conleth Feighery,[5] Gina Gregorini,[6] Wolfgang L. Gross,[7] Raashid Luqmani,[8] and David R. W. Jayne,[9] for the European Vasculitis Study Group




**寛解率**

MTXとpoCYで有意差なし




**再燃free率**

MTXが有意に再燃しやすい
(p=0.023)

- Unblinded, multicenter, RCT, 18M観察
- 新規非重篤AAV 100人(Cr<150μmol/l [1.74mg/dl])を, MTX群(20-25mg/w)とpoCY群(2mg/kg/d)にランダム化割付し寛解導入. 両薬とも12Mで漸減中止. PSL量は双方同じ.
- MTX群(51人): 6M 寛解率 89.8% [poCY非劣性]
  18M 再発率 69.5% [poCYより再燃率高い]
  特に重症例と肺病変で再燃率↑
- poCY群(49人)：6M 寛解率 93.5%
  18M 再発率 46.5%
- Primary endpoint：6M寛解率
- 有害事象：MTX/poCYとも2人死亡. 血球減少はpoCYで多く肝機能はMTXで多い.
- 結論：MTXはpoCY寛解導入と早期は置換可能.
  MTXは肺病変と重症例で効果低く再燃しやすい.
  双方再燃率高く12M≧治療が必要.

寛解導入
MMF vs IVCY

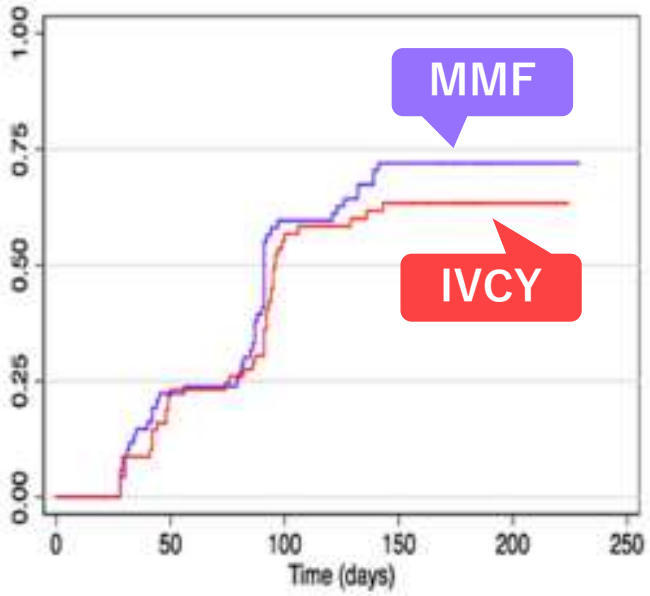
# MYCYC (2019)

[Ann Rheum Dis. 2019;78(3):399-405.]

Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial

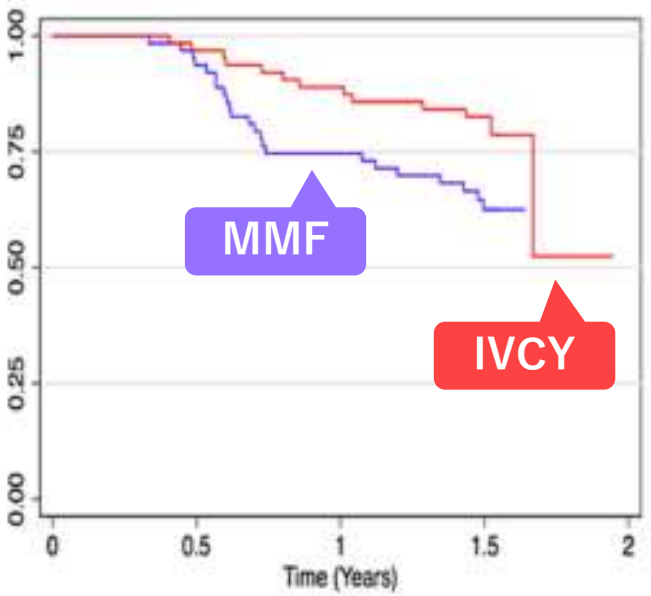
Rachel B Jones,[1] Thomas F Hiemstra,[2,3] Jose Ballarin,[4] Daniel Engelbert Blockmans,[5] Paul Brogan,[6,7] Annette Bruchfeld,[8] Maria C Cid,[9] Karen Dahlsveen,[1] Janak de Zoysa,[10,11] Georgina Espigol-Frigolé,[9] Peter Lanyon,[12] Chen Au Peh,[13] Vladimir Tesar,[14] Augusto Vaglio,[15,16] Michael Walsh,[17] Dorothy Walsh,[1] Giles Walters,[18] Lorraine Harper,[19] David Jayne,[1,2] for the European Vasculitis Study Group (EUVAS)

**寛解率**




寛解導入率では
MMFはIVCYに非劣性

**再燃free率**




再燃率は
MMFはIVCYより高い

- Open-label, multicenter, Randomized non-inferiority trial
- 新規診断AAV 140人→ MMF (2g, 4wで改善なければ3gまで許容)とIVCY (15mg/kg/2-3w, CYCLOPSと同じ)に振分け寛解導入
- 3-6wで寛解後AZA 2mg/kgで維持, 18M観察.
- AAV= GPA or MPA, ANCA+or病理
- MMF群(70人): 67%寛解, 再燃33%(p=0.049でCYより再燃率高い)
- IVCY群(67人): 61%寛解, 再燃19%
- MPO-ANCA患者: 再燃率 MMF 15%, CY 12%
- PR3-ANCA患者: 再燃率 MMF 48%, CY 24%
- 結論: MMFは寛解導入にIVCYと非劣性だが, 再燃率は高い. 特にPR3-ANCA患者はMMFで再燃する.

# Changing landscape of immunosuppression in ANCA-associated vasculitis

Ann Rheum Dis 2020;79:e59.

# MYCYCを受けた寛解導入の提案 (correspondence)

**Table 1** Possible tailored regimens of remission induction treatment in patients with AAV

| | Non-severe AAV | Severe AAV |
|---|---|---|
| Proteinase-3 ANCA | Methotrexate* or rituximab | Rituximab† or cyclophosphamide |
| MPO-ANCA | Methotrexate* or MMF or rituximab | Cyclophosphamide or rituximab† or MMF† |
| ANCA-negative | Methotrexate* or cyclophosphamide | Cyclophosphamide |

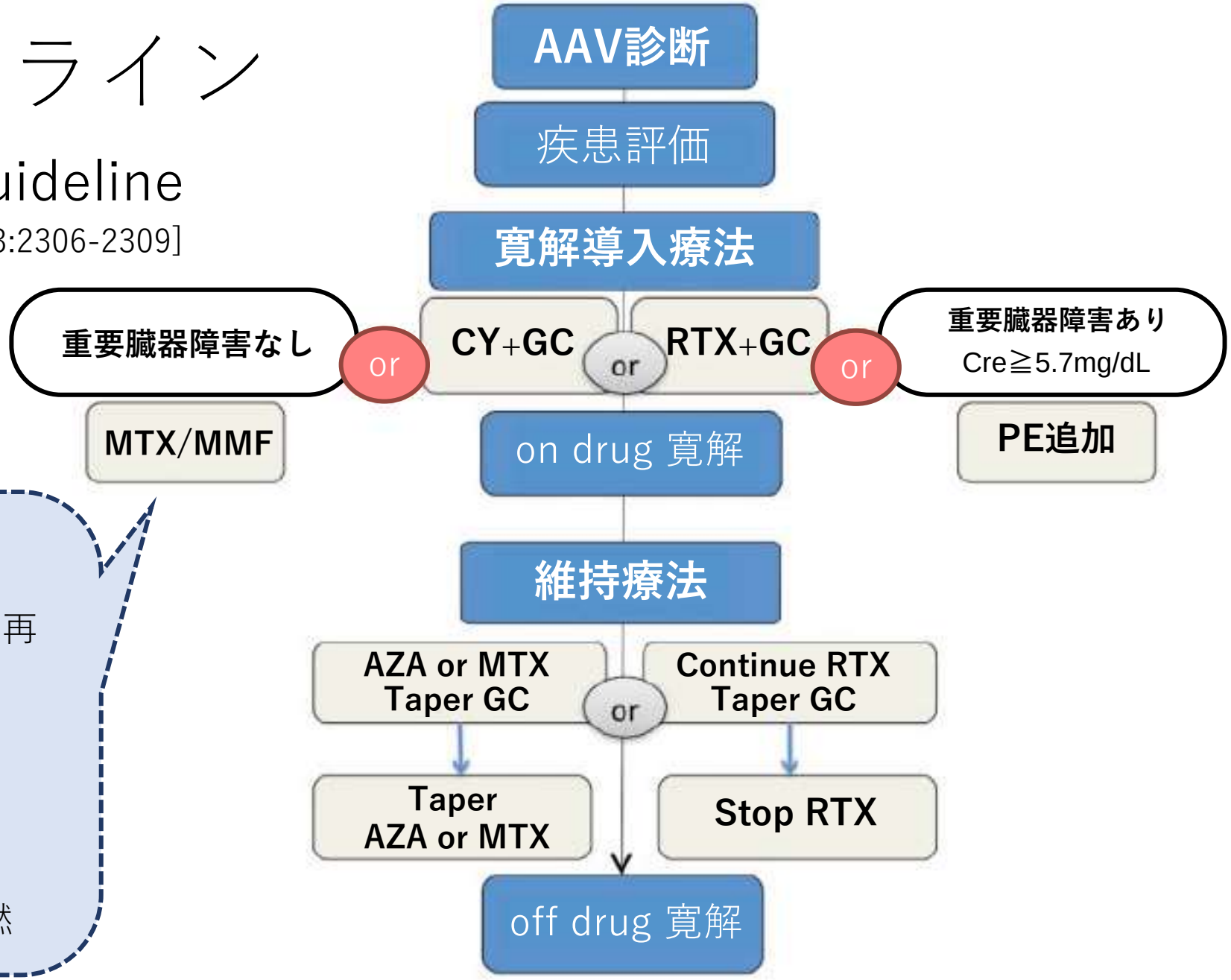
- MYCYCの結果を受けた読者の個人的なletter(露)
- MPO-ANCA (再燃リスク低い)ではMMFは選択肢
- PR3-ANCA (再燃リスク高い)はMMFを避ける（MYCYC)
- ANCA陰性の方が再燃しない

- Severe AAVはCY or RTX
- MMFは腎機能障害や不妊などのリスクは低い
- MMFは再燃例でも使わない．維持では使わない(IMPROVE).
- RTXをANCA-で使わないのは？本文中記載はない

# AAV治療ガイドライン

## 2014 BSR and BHPR guideline

[Rheumatology 2014;53:2306-2309]




**NORAM (2005)**

- MTX = poCY(寛解導入率同じ).
- MTXは肺病変と重症例で効果低く再燃しやすい.
- 双方再燃率高く12M以上治療必要

**MYCYC (2019)**

- MMF=IVCY (寛解導入率非劣性)
- MMF<IVCY (再燃率高い)
- 特にPR3-ANCA患者はMMFで再燃

寛解導入
PE

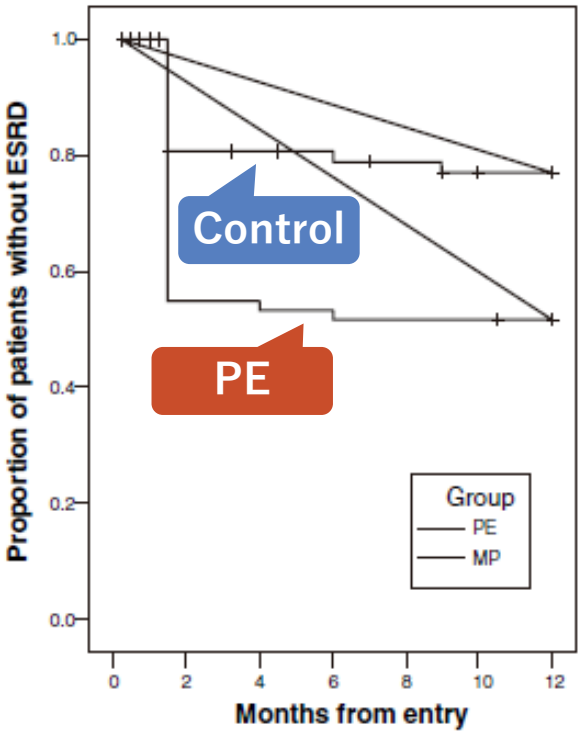
# MEPEX(2007)

[J Am Soc Nephrol. 2007;18(7):2180-8.]

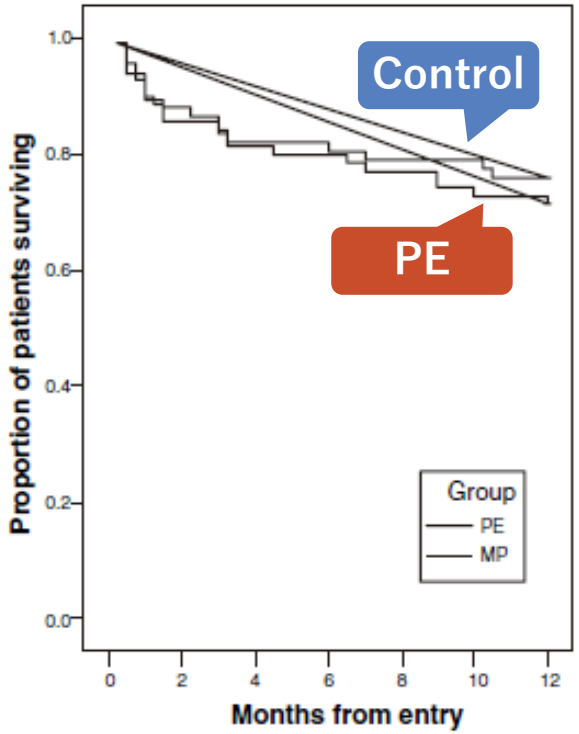
## Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,‖ Loic Guillevin,¶ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,‡‡ Kerstin W. Westman,§§ Fokko J. van der Woude,‖‖ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

**ESRD率はPEで改善**




**Survivalに差はない**



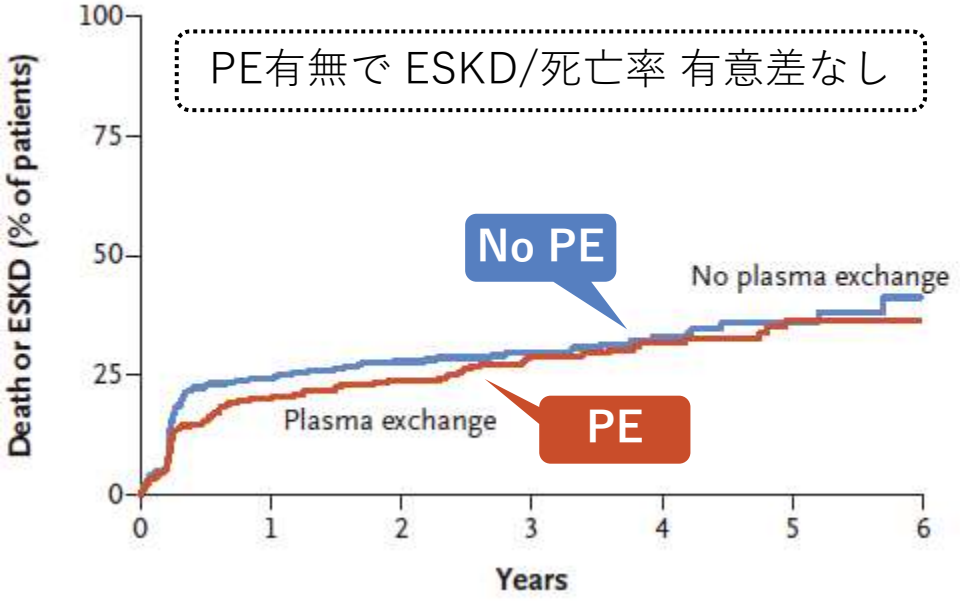

- Open-label, multicenter, Randomized trial
- 腎生検で確定した新規AAV 137人, 重度腎障害 (Cr > 5.8mg/dL[500μmol/l])のPEの評価.
- PE群 (70人), Control群 (67人; mPSL pulse(3g)) 両群とも他の治療は同量のPSL
- Primary endpoint：3M後透析不要率
- Secondary endpoint：1年後のESRD/生存率
- 3M: 透析不要な生存率はPEが高い (PE 69%, Control 49%, p=0.002).
- 1年: ESRDになる率はPEが低い (PE 19%, Control 43%, 24%減少).
- 1年: 重篤な有害事象同じ (PE 50%, Control 48%)
- 1年: 生存率は同じ (PE 73%, Control 76%)
- 結論: PEはmPSL pulseに比べ腎予後を改善するが, 生存率は改善しない.

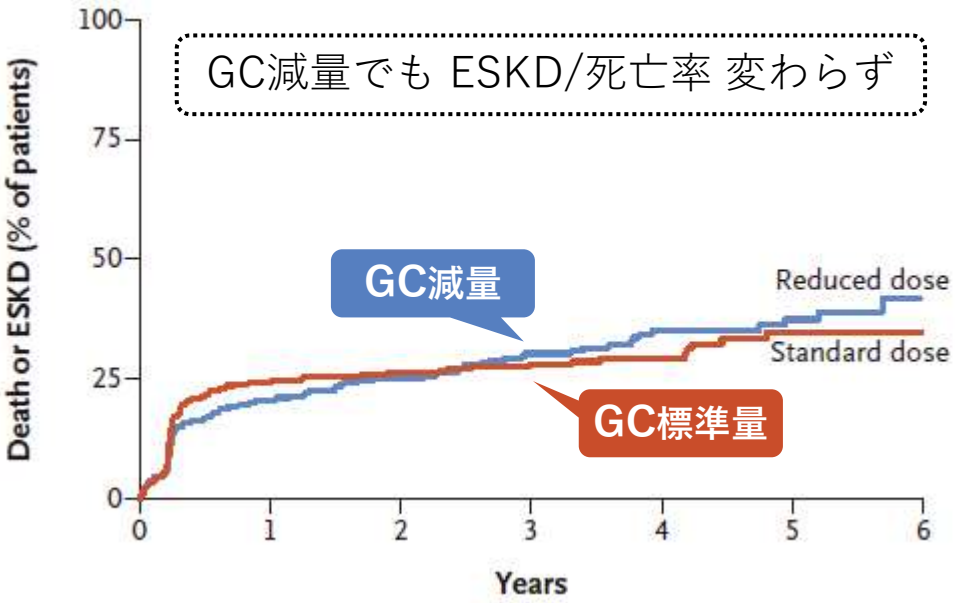
寛解導入
PE

# PEXIVAS(2020)

[N Engl J Med. 2020;382(7):622-631.]

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis




- Open-label, multicenter, 2X2要因デザイン[PE有無 x GC標準・減量群], Randomized trial(7年観察)
- 対象: 新規or再発の重症AAV704人(GPA/MPA, MPO+かPR3+, eGFR<50 or 肺胞出血), PE+352人/PE-352人. GC標準325人/GC減330人.
- 介入: PE有無 [14日間に7回PE]とGC標準/減量群の4群. CY(15mg/kg, 2-3w, X10)かRTX(375mg/$m^2$/w X4)の加療は施設に委託. 全員mPSL pulse(1-3g)
- GC標準群＝3wから減量/23wで5mg.
  GC減量群＝標準の50%で開始/15-19wで5mg, 積算 60%.

| Week | Standard | | | Reduced dose | | |
|---|---|---|---|---|---|---|
| | <50 kg | 50-75 kg | >75 kg | <50 kg | 50-75 kg | >75 kg |
| | pulse | pulse | pulse | pulse | pulse | pulse |
| 1 | 50 | 60 | 75 | 50 | 60 | 75 |
| 2 | 50 | 60 | 75 | 25 | 30 | 40 |
| 3-4 | 40 | 50 | 60 | 20 | 25 | 30 |
| 5-6 | 30 | 40 | 50 | 15 | 20 | 25 |
| 7-8 | 25 | 30 | 40 | 12.5 | 15 | 20 |
| 9-10 | 20 | 25 | 30 | 10 | 12.5 | 15 |
| 11-12 | 15 | 20 | 25 | 7.5 | 10 | 12.5 |
| 13-14 | 12.5 | 15 | 20 | 6 | 7.5 | 10 |
| 15-16 | 10 | 10 | 15 | 5 | 5 | 7.5 |
| 17-18 | 10 | 10 | 15 | 5 | 5 | 7.5 |
| 19-20 | 7.5 | 7.5 | 10 | 5 | 5 | 5 |
| 21-22 | 7.5 | 7.5 | 7.5 | 5 | 5 | 5 |
| 23-52 | 5 | 5 | 5 | 5 | 5 | 5 |
| >52 | Investigators' Local Practice | | | Investigators' Local Practice | | |

- 結論1: PEの有無でESKD or 死亡率に有意差がない (PE+ 28.4%, PE- 31.0%). PE追加の意義乏しい
- 結論2: GC減量群でESKD or 死亡率は非劣性(標準 25.5%, 減量 27.9%). GC減量群で重篤な感染症減少(incidence rate ratio 0.69)

# PEXIVAS ステロイド減量Protocolの拡大

**Table 1** Dosing for oral Glucocorticoids in the standard and reduced dose limbs from trial start

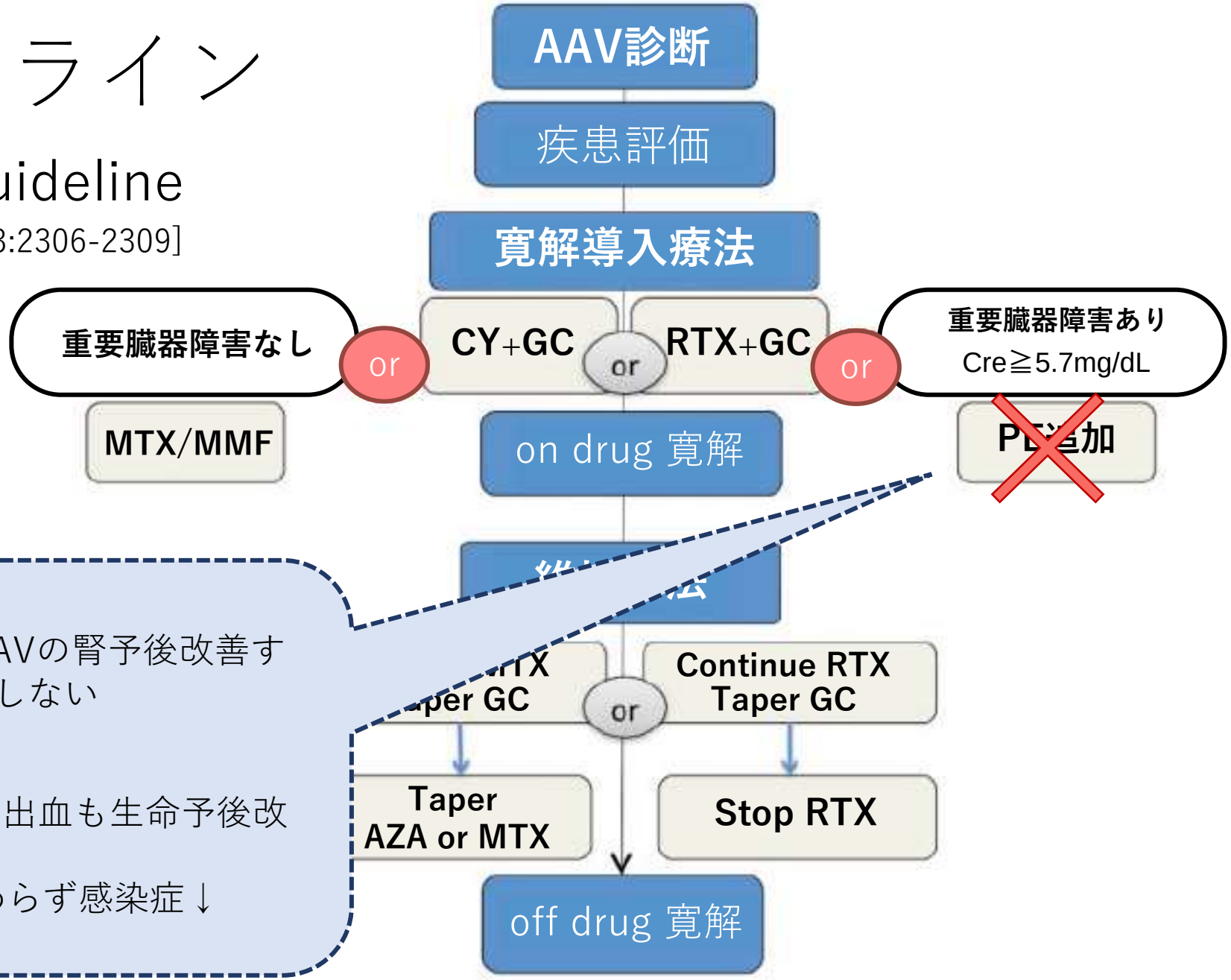
| Week | Standard | | | Reduced Dose | | |
|---|---|---|---|---|---|---|
| | <50 kg | 50-75 kg | >75 kg | <50 kg | 50-75 kg | >75 kg |
| | pulse | pulse | pulse | pulse | pulse | pulse |
| 1-2 | 50 | 60 | 75 | 25 | 30 | 40 |
| 3-4 | 40 | 50 | 60 | 20 | 25 | 30 |
| 5-6 | 30 | 40 | 50 | 15 | 20 | 25 |
| 7-8 | 25 | 30 | 40 | 12 | 15 | 20 |
| 9-10 | 20 | 25 | 30 | 10 | 12 | 15 |
| 11-12 | 15 | 20 | 25 | 7 | 10 | 12 |
| 13-14 | 12 | 15 | 20 | 6 | 7 | 10 |
| 15-16 | 10 | 10 | 15 | 5 | 5 | 7 |
| 17-18 | 10 | 10 | 15 | 5 | 5 | 7 |
| 19-20 | 7 | 7 | 10 | 5 | 5 | 5 |
| 21-22 | 7 | 7 | 7 | 5 | 5 | 5 |
| 23-52 | 5 | 5 | 5 | 5 | 5 | 5 |
| >52 | Investigators' Local Practice | | | Investigators' Local Practice | | |

- 全員mPSL pulse(1-3g).
- GC標準群＝3wから減量/23wで5mg.
- GC減量群＝標準群の50%減量から開始/15-19wで5mg, 積算で標準群の 60%.

# AAV治療ガイドライン

## 2014 BSR and BHPR guideline

[Rheumatology 2014;53:2306-2309]




**MEPEX (2007)**

- PE：重度腎障害AAVの腎予後改善するが生命予後改善しない

**PEXIVAS (2020)**

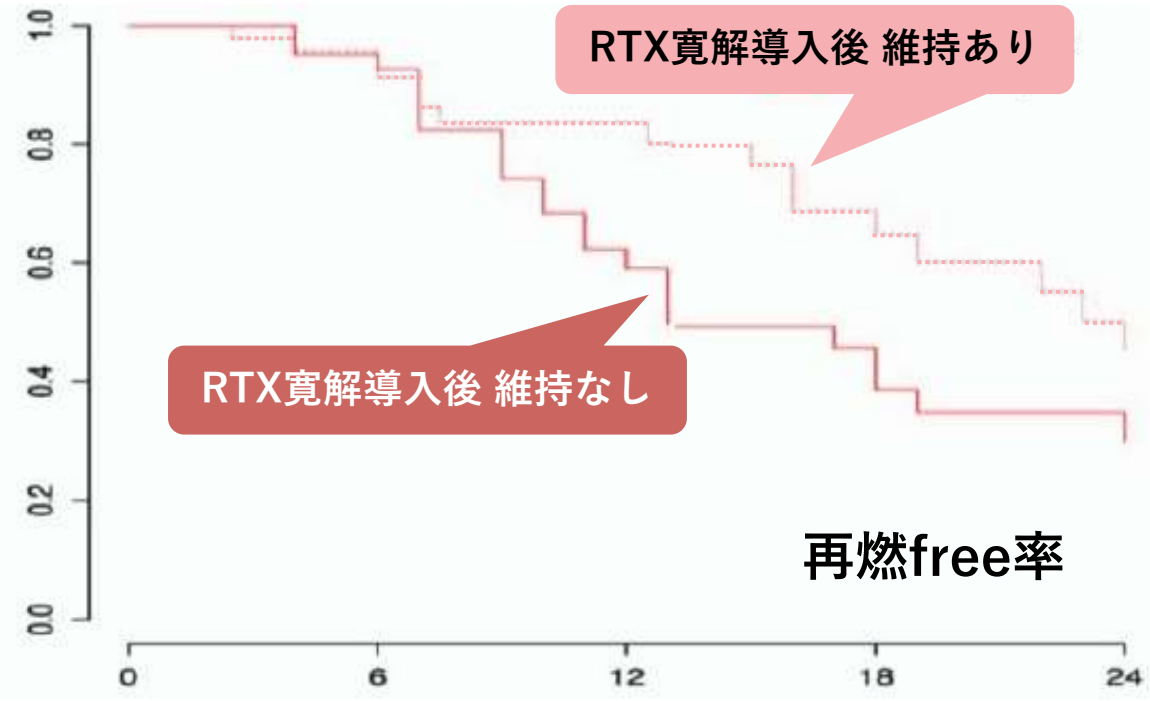
- PE：腎障害も肺胞出血も生命予後改善効果なし
- GC減量で予後変わらず感染症↓

# RTXによる寛解導入後 維持療法は必要か？

Rituximab With or Without a Conventional Maintenance Agent in the Treatment of Relapsing Granulomatosis With Polyangiitis (Wegener's)

A Retrospective Single-Center Study

[Arthritis Rheumatol. 2014;66(10):2862-70]




- Single center, retrospective study.
- RTXによる寛解導入後89症例→維持療法(AZA/MTX/MMF)あり群(n=42)となし群(n=47)で比較
- 維持あり群は維持療法なし群より再燃少ない (p=0.04, HR 0.56).
- 有害事象は差がない

↓

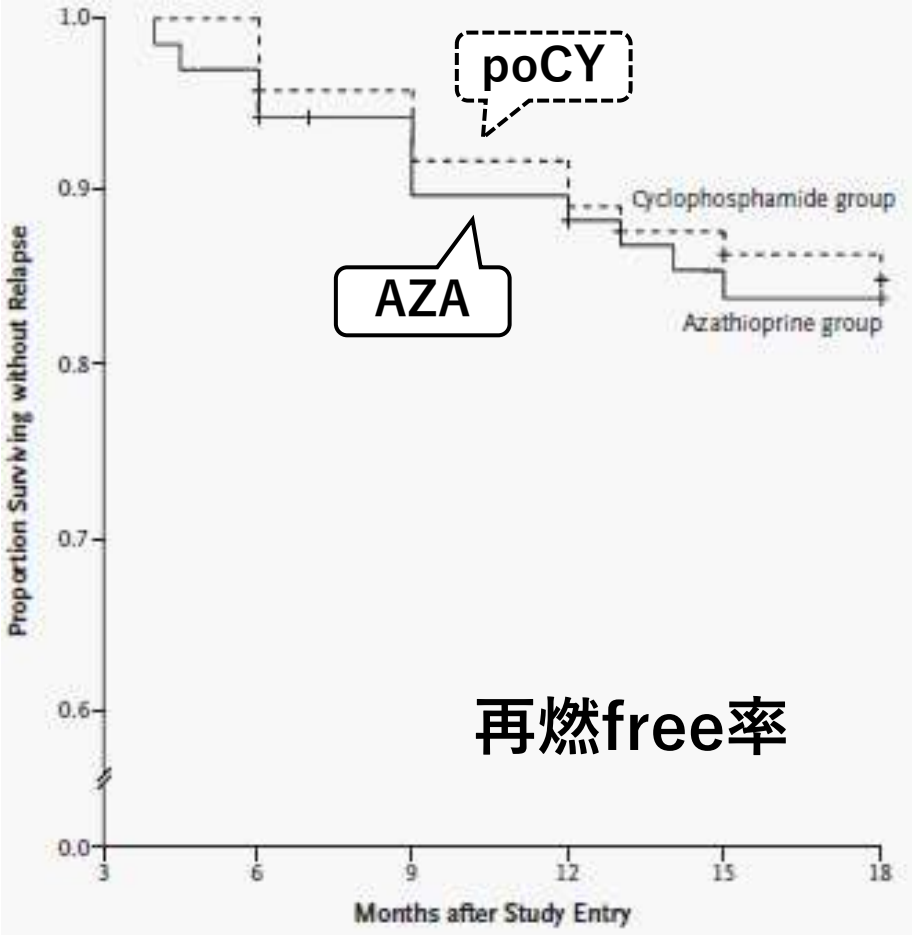
∴ RTX寛解後, 維持療法は必要

維持 po
poCY vs AZA

# CYCAZAREM(2003)

[N Engl J Med 2003;349:36-44.]

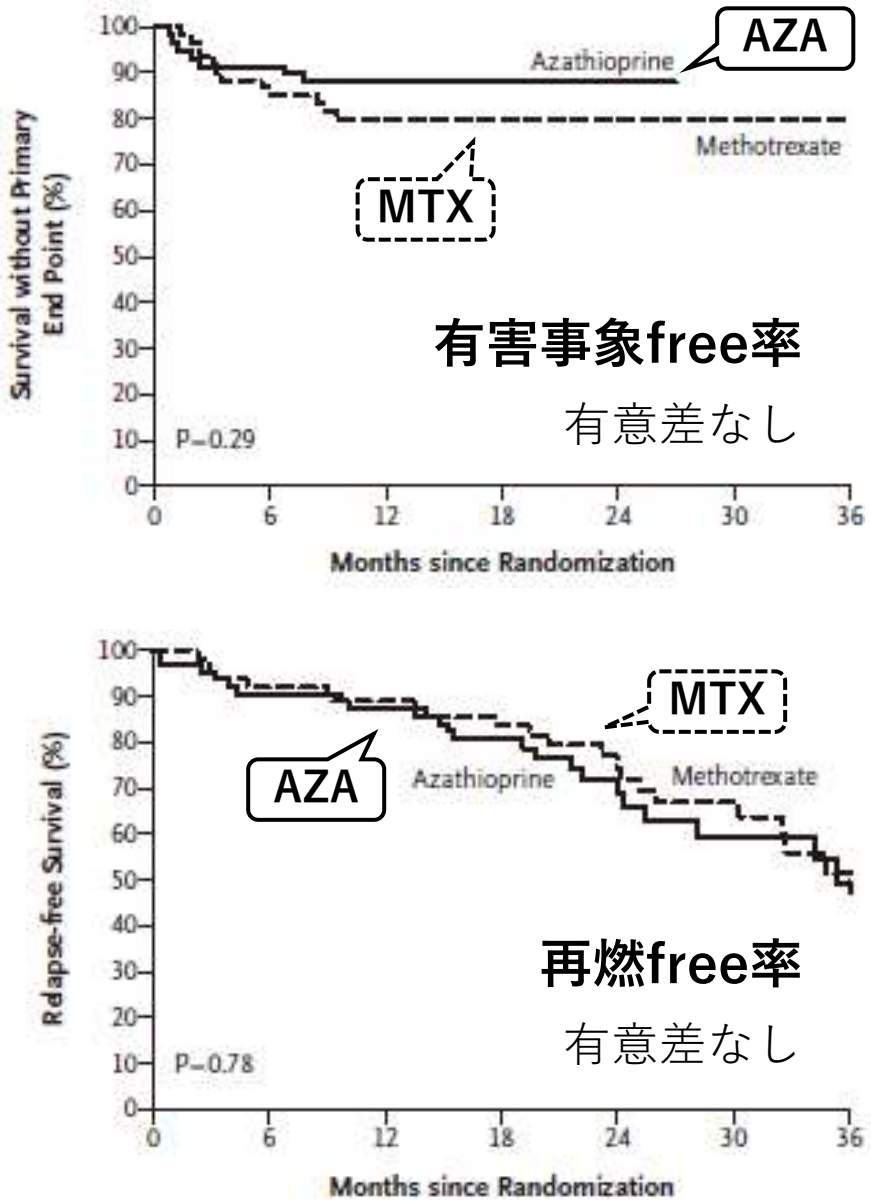
A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies




- Unblinded, multicenter, RCT, 18M観察
- poCY+PSLで寛解が得られた新規generalized非重篤AAV 144人(Cr<500μmol/l [5.8mg/dl])を，poCY群(1.5mg/kg/d)とAZA群(2mg/kg/d)にランダム化割付し維持療法. PSLは継続.
- 再燃がend point.
- poCY群(73人): 13.7%が再燃, 有害事象10%
- AZA群(71人)：15.5%が再燃 (p=0.65), 有害事象11% (p=0.94)
- 再燃率はMPA(8%)がGPA(18%)より有意に低かった(p=0.03)
- 結論：generalized AAVではpoCYでの寛解導入後AZAで維持しても再燃率は上昇しない.

# WEGENT(2008)

[N Engl J Med 2008;359:2790-803.]



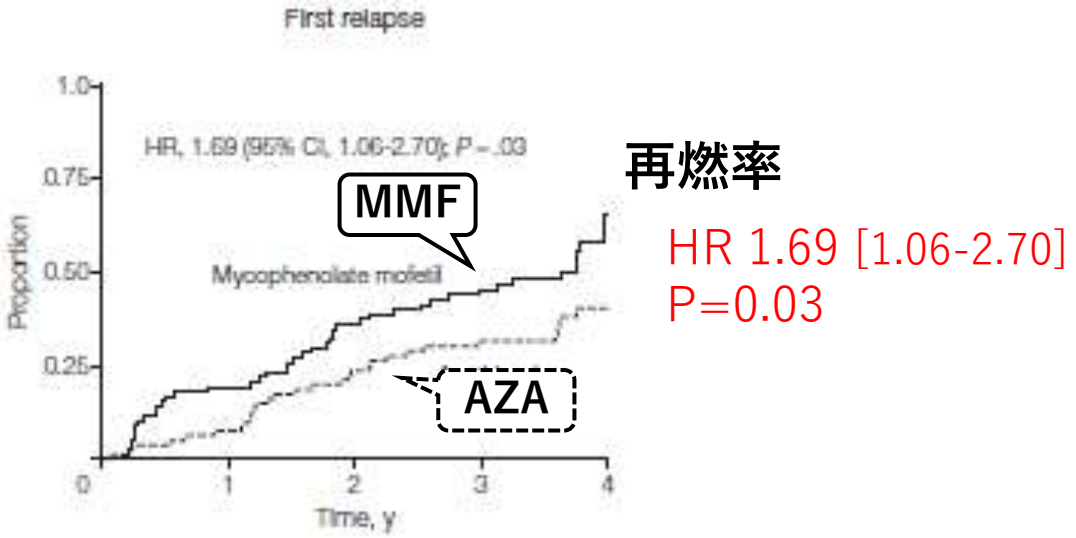

- Open-label, multicenter, RCT
- 仮説：MTXがAZAより維持療法中の安全性が高い
- IVCY+PSLで寛解が得られた新規AAV 126人(GPAかMPA)を, MTX群(0.3mg/kg/w→25mg/wに漸増)とAZA群(2mg/kg/d)にランダム化割付し12M維持療法.
- Primary end point: 有害事象や死亡での治療中断
- MTX群(63人): 12人中止, 21人再燃, 1人死亡
- AZA群(63人)：7人中止, 23人再燃
- 維持療法中止後73%が再燃した.
- 有害事象に有意差なし. 再燃率に有意差なし.
- 結論：MTXがAZAより安全性が高いという仮説を立てていたが, 差がないことが明らかになった. AAV維持療法として両者は同等.

# Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Controlled Trial

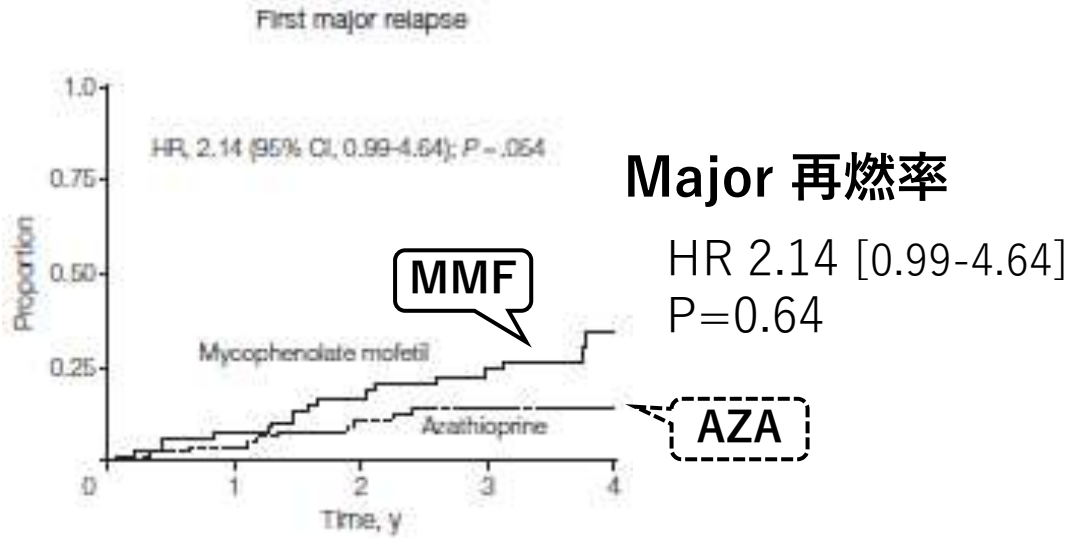
# IMPROVE(2010)

[JAMA. 2010;304(21):2381-2388.]




**再燃率**

HR 1.69 [1.06-2.70]
P=0.03




**Major 再燃率**

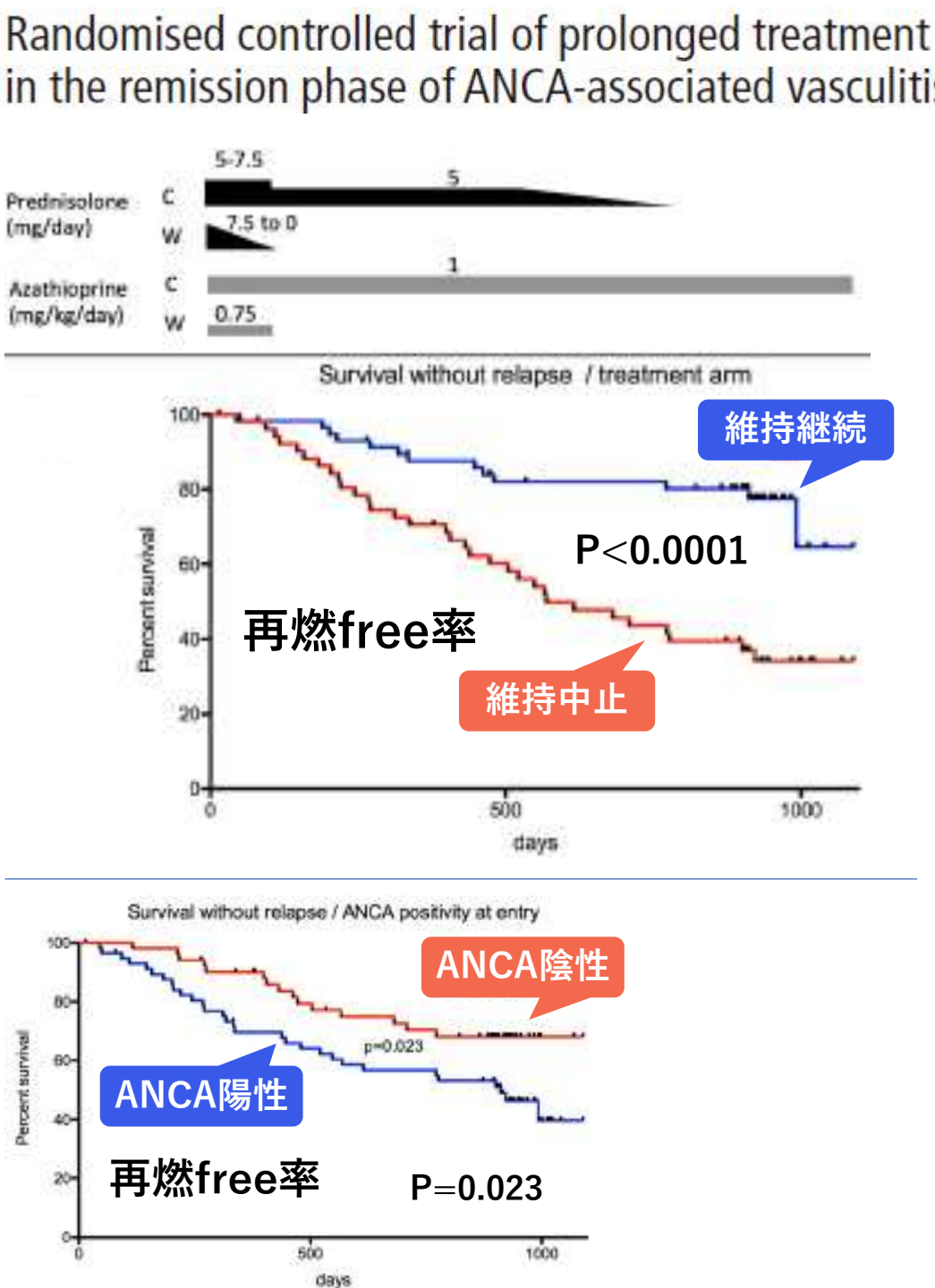
HR 2.14 [0.99-4.64]
P=0.64

- Open-label, multicenter, RCT, 42M観察
- 仮説：MMFがAZAより再燃予防に有効
- [IVCY or poCY]+PSLで寛解が得られた新規AAV 156人(GPAかMPA)を, MMF群(2000mg)とAZA群(2mg/kg/d)にランダム化割付.
- Primary end point: 再燃率
- MMF群(76人): 42人再燃(p=0.03), 8人SAE
- AZA群(80人)：30人再燃, 13人SAE
- MMFがAZAより再燃が多い. 有害事象に差なし.
- 結論：MMFはAZAよりAAVの維持効果が劣っている.

維持
継続期間

# REMAIN(2017)

[Ann Rheum Dis 2017;76:1662–1668.]




- Open-label, multicenter, RCT(36M観察)
- CY+PSLで寛解しAZA+PSLで維持した Dx18-24M AAV[53%がAAV⁺]→ Dx48M 継続群と24M中止群に1:1振分け
- 継続群(n85): 再燃22%
- 中止群(n85): 再燃63% (OR 5.96, p<0.0001)
- ANCA陽性の方が再燃する(55% vs 29%)
- 結論：AZA維持治療は特にANCA陽性例では診断48カ月までは継続するべき. 維持療法は腎生存率も上げる.

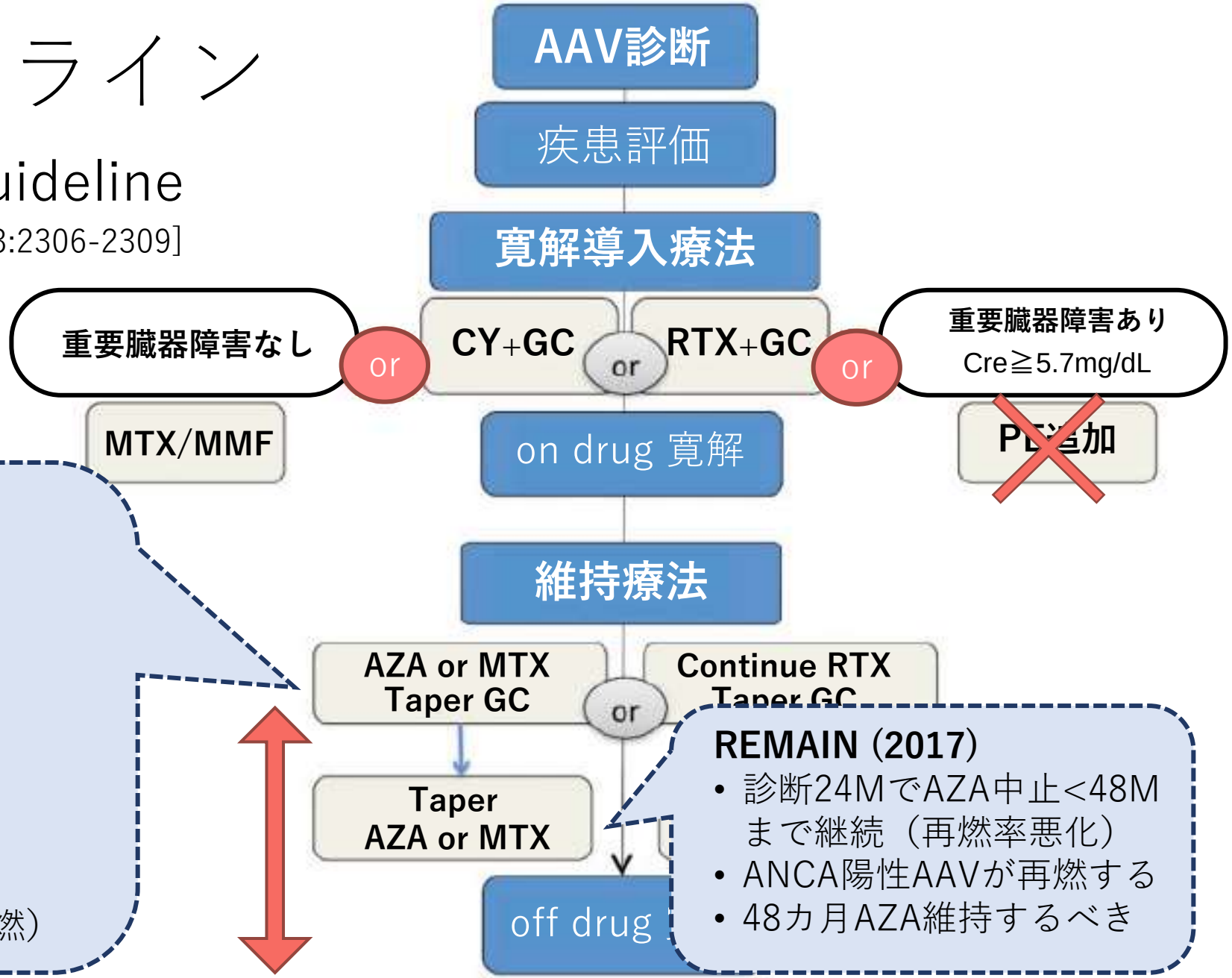
# REMAINのdiscussion記載から

- AZA維持しても5年で38％が再燃(CY寛解), 32%再燃(RTX寛解)
- 維持Txの再燃抑制力：MTX=AZA>MMF>>ETN
- 最近：RTX>AZA (MAINRITSAN 2014)

# AAV治療ガイドライン

## 2014 BSR and BHPR guideline

[Rheumatology 2014;53:2306-2309]




**CYCAZAREM (2003)**
- poCY=AZA（寛解維持率同等）
- 安全性も同等
- GPAがMPAより有意に再燃する

**WEGENT (2008)**
- MTX=AZA（寛解維持率同等）
- 安全性も同等

**IMPROVE (2010)**
- AZA＞MMF（MMFは有意に再燃）

**REMAIN (2017)**
- 診断24MでAZA中止<48Mまで継続（再燃率悪化）
- ANCA陽性AAVが再燃する
- 48カ月AZA維持するべき

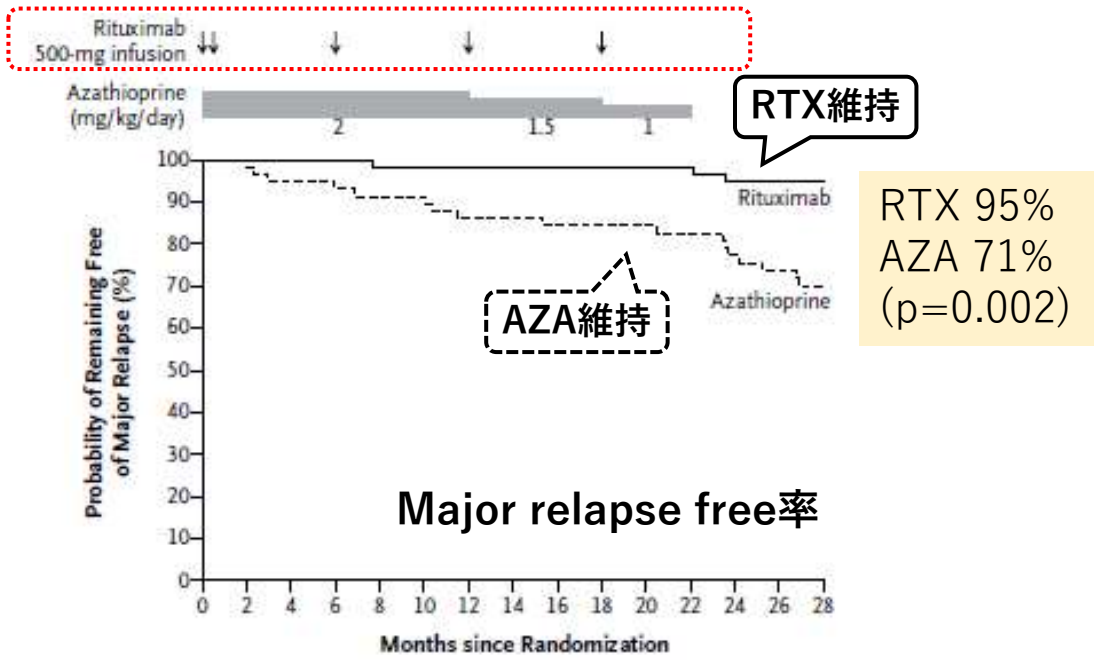
# MAINRITSAN1(2014)

[N Engl J Med 2014;371:1771-80.]

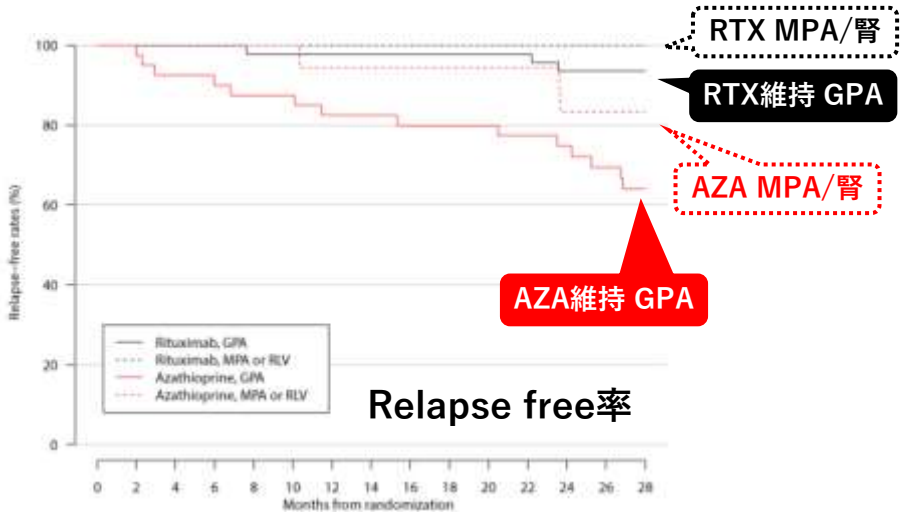
維持
RTX vs AZA

## Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*




RTX 95%
AZA 71%
(p=0.002)




- Open-label, multicenter, RCT(28Mで評価)
- CY(0.6g/m$^2$ 0/2/4w, 0.7g/m$^2$/3w x3-6, 4-6Mで寛解になるまで)+GC(pulse+ 1mg/kg)で寛解した初発/再燃AAV(GPA87/MPA23/腎AAV5)→ RTX or AZA維持比較
- RTX群(57): RTX 500mgを day0, d14と6M, 12M, 18M
- AZA群(58): 2mg/kg 12M→1.5mg/kg 6M→1mg/kg 4M
- Primary endpoint: 28ヶ月までのmajor relapse率
- Major relapse: AZA 29%, RTX 5% [HR 6.61, p=0.002]
- Minor relapse: AZA 16%, RTX 11% (p=0.43)
- 有害事象：重篤な感染 AZA 14%, RTX 19%
- 結論: AAVの維持はRTXがAZAより優れている(少なくともPR3-ANCA$^+$ ). 副作用に違いなし.
- 批判的意見: AZA減量中止プロトコルはCYCAZAREM等と違い妥当性の保証が不足. TPMT活性によってAZAの有効性が変わるかも知れない.

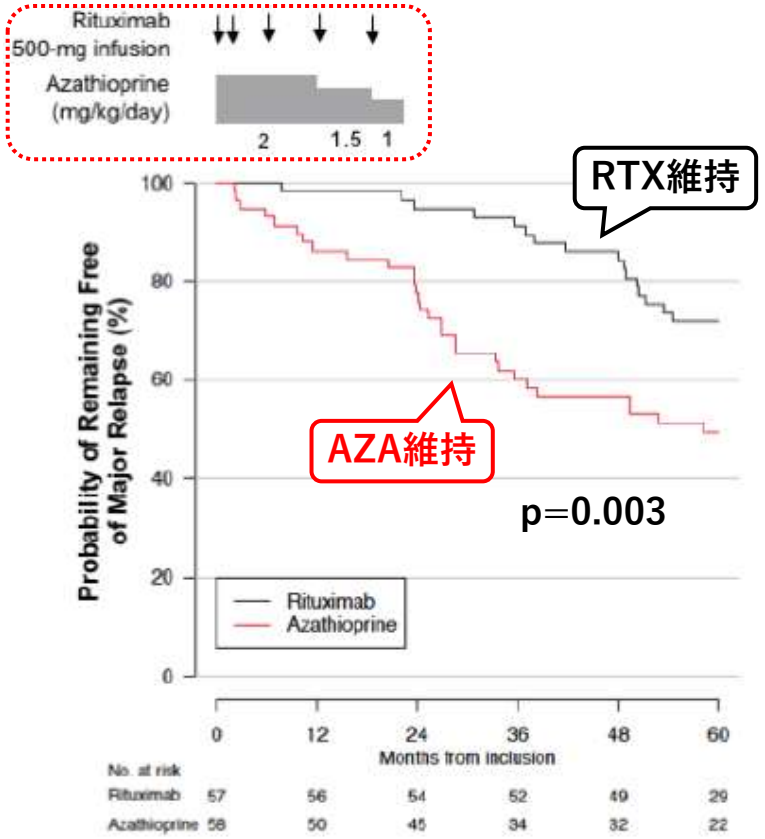
# MAINRITSAN1 長期(2018)

[Ann Rheum Dis 2018;77:1151–1157.]

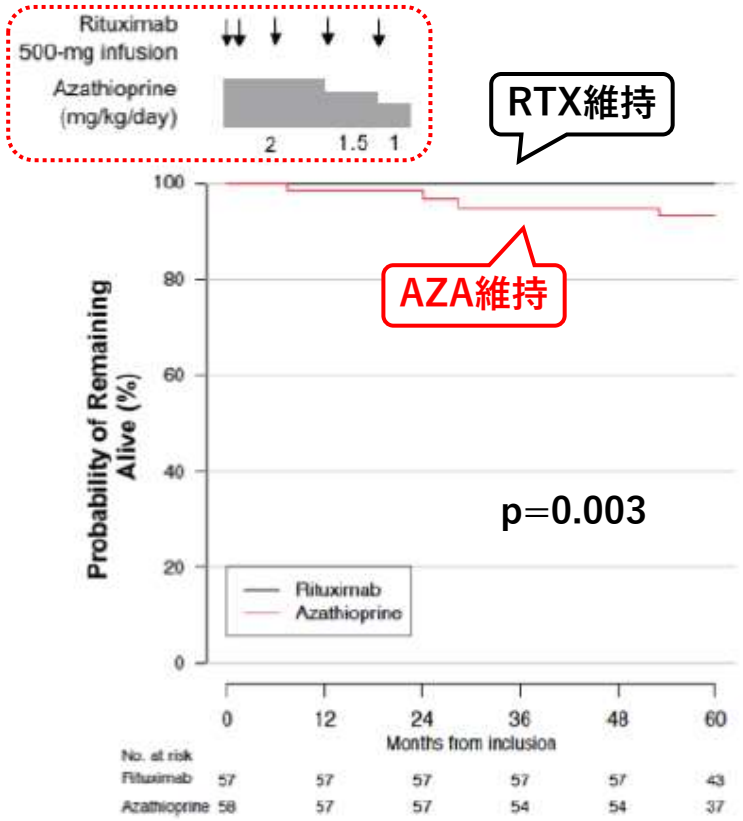
Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides

Benjamin Terrier,[1] Christian Pagnoux,[1,2] Élodie Perrodeau,[3] Adexandre Karras,[4] Chahera Khouatra,[5] Olivier Aumaître,[6] Pascal Cohen,[1] Olivier Decaux,[7] Hélène Desmurs-Clavel,[8] François Maurier,[9] Pierre Gobert,[10] Thomas Quémeneur,[11] Claire Blanchard-Delaunay,[12] Bernard Bonnotte,[13] Pierre-Louis Carron,[14] Eric Daugas,[15] Marize Ducret,[16] Pascal Godmer,[17] Mohamed Hamidou,[18] Olivier Lidove,[19] Nicolas Limal,[20] Xavier Puéchal,[1] Luc Mouthon,[1] Philippe Ravaud,[3] Loïc Guillevin,[1,21] on behalf of the French Vasculitis Study Group

**Major relapse free率**




**Overall survival rate**



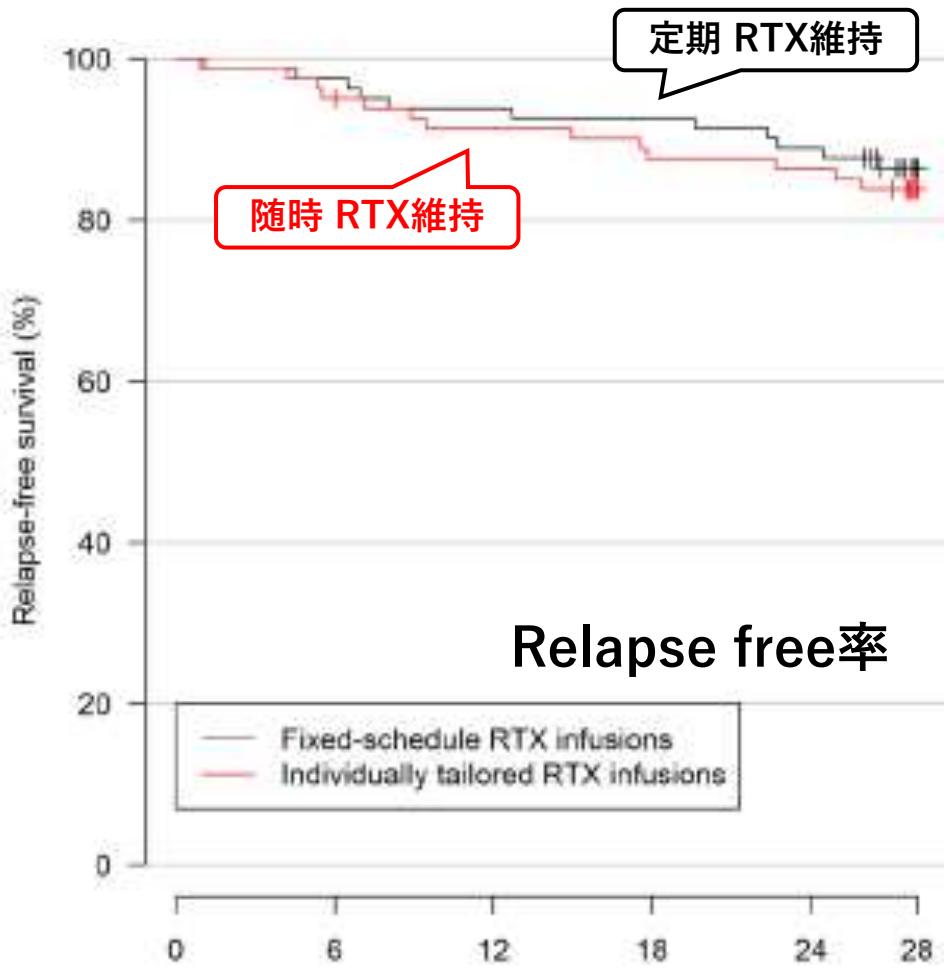

- MAINRITSAN1 5年観察(60M)
- CYで寛解後, RTX維持(6か月ごと18Mまで)とAZA維持(22Mで終了)比較を60Mまで観察
- Major relapse free: AZA 49.4%, RTX 71.9% [p=0.003]
- Survival: AZA 93%, RTX 100% (p=0.045)
- GC積算量は同等
- 無症状期間はRTXが12.6M長い
- 再燃リスク因子：PR3-ANCA陽性, AZA維持
- 結論: AAVの維持はRTXがAZAより長期でも優れている.

維持 RTX
定期 vs 随時

# MAINRITSAN2(2018)

[Ann Rheum Dis 2018;77:1144–1150.]

Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)




- Open-label, multicenter, RCT(28Mで評価)
- 寛解した初発/再燃AAV(GPA117/MPA45)(寛解Txは CY100/ RTX61/ MTX 1)→ 定期RTX or CD19⁺/ANCAに応じた随時Tailored RTX維持比較
- 定期RTX群(81): RTX 500mgをday0, d14と6M, 12M, 18M
- 随時Tailored RTX群(81): CD19⁺Bが出現 or ANCA上昇時にRTX 500mg投与
- Primary endpoint: 28ヶ月までの再燃数/BVAS>0
- 再燃：定期 9.9%, Tailored 17.3% (p=0.22) 同等
- 投与回数: 定期 381回, Tailored 248回とTailoredの方が回数が少ない.
- 結論: RTX維持は定期投与とTailoredで再燃率に差がなかった. Tailoredの方が投与回数は少なかった.

維持(RTX後)
RTX vs AZA

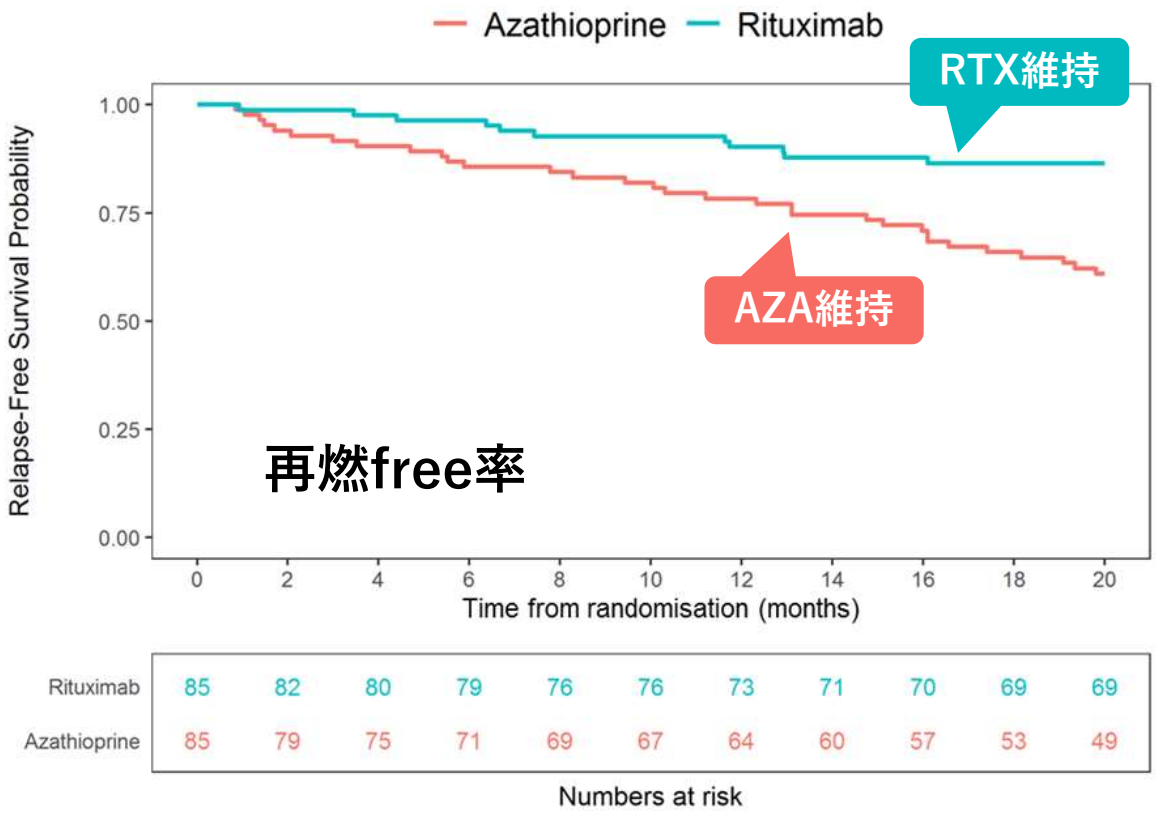
# RITAZAREM(2019)

[ACR 2019 Abstract number: 806.]

ABSTRACT NUMBER: 806

## A Randomized, Controlled Trial of Rituximab versus Azathioprine After Induction of Remission with Rituximab for Patients with ANCA-associated Vasculitis and Relapsing Disease

Rona Smith[1], David Jayne [2] and Peter Merkel [3], [1]University of Cambridge, Cambridge, England, United Kingdom, [2]Vasculitis and Lupus Clinic, Addenbrooke's Hospital, University of Cambridge, UK, Cambridge, United Kingdom, [3]University of Pennsylvania, Philadelphia

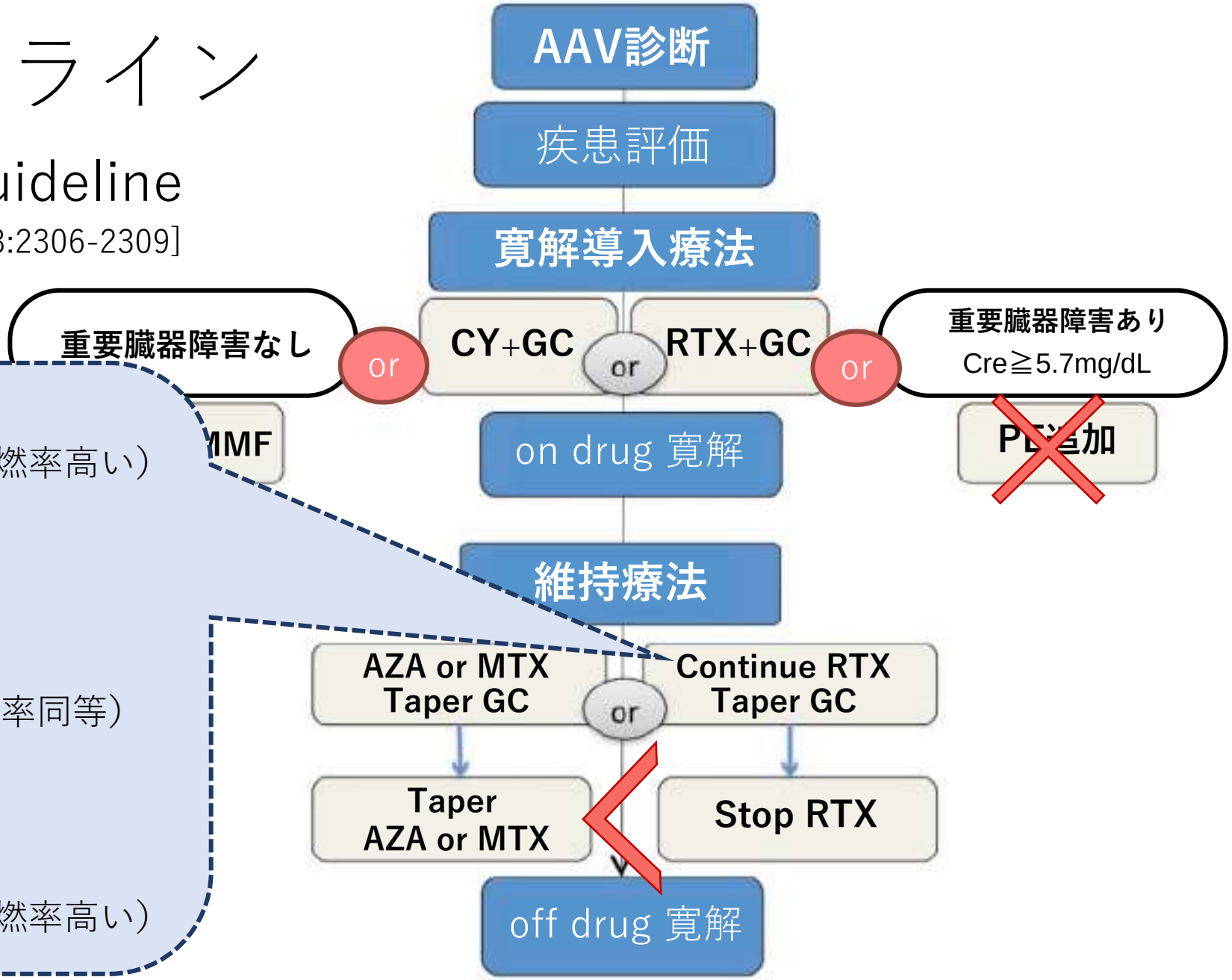



- Open-label, multicenter, RCT(36M観察)
- 再燃AAV [72% PR3-ANCA, 28% MPO-ANCA] RTX+ GCで寛解導入, 4M後→ RTX or AZA維持の比較
- RTX維持群(n85): RTX 1000mg/4M x 5回
- AZA維持群(n85): AZA 2mg/kg/d
- 結果：RTX維持投与による再燃予防効果はAZAに比べて有意に優れている（HR 0.36 [95% CI 0.23-0.57], p<0.001）
- 有害事象：IgG↓と感染, 両者に差はない
- 結論：再燃のAAVにおけるRTX寛解後の維持療法は, RTXがAZAより優れている.

# AAV治療ガイドライン

## 2014 BSR and BHPR guideline

[Rheumatology 2014;53:2306-2309]




**MAINRITSAN1 (2014)**
- RTX維持＞AZA維持（AZAが再燃率高い）
- AZA群漸減中止に批判
- GPAの再燃率特に高い
- 寛解療法はCY

**MAINRITSAN2 (2018)**
- RTX　定期=Tailored投与（再燃率同等）
- 寛解療法はCY/RTX/MTX混合

**RITAZAREM (2019)**
- RTX寛解後の維持
- RTX維持＞AZA維持（AZAの再燃率高い）

# CY/RTX/PE/MMF/AZA以外の治療

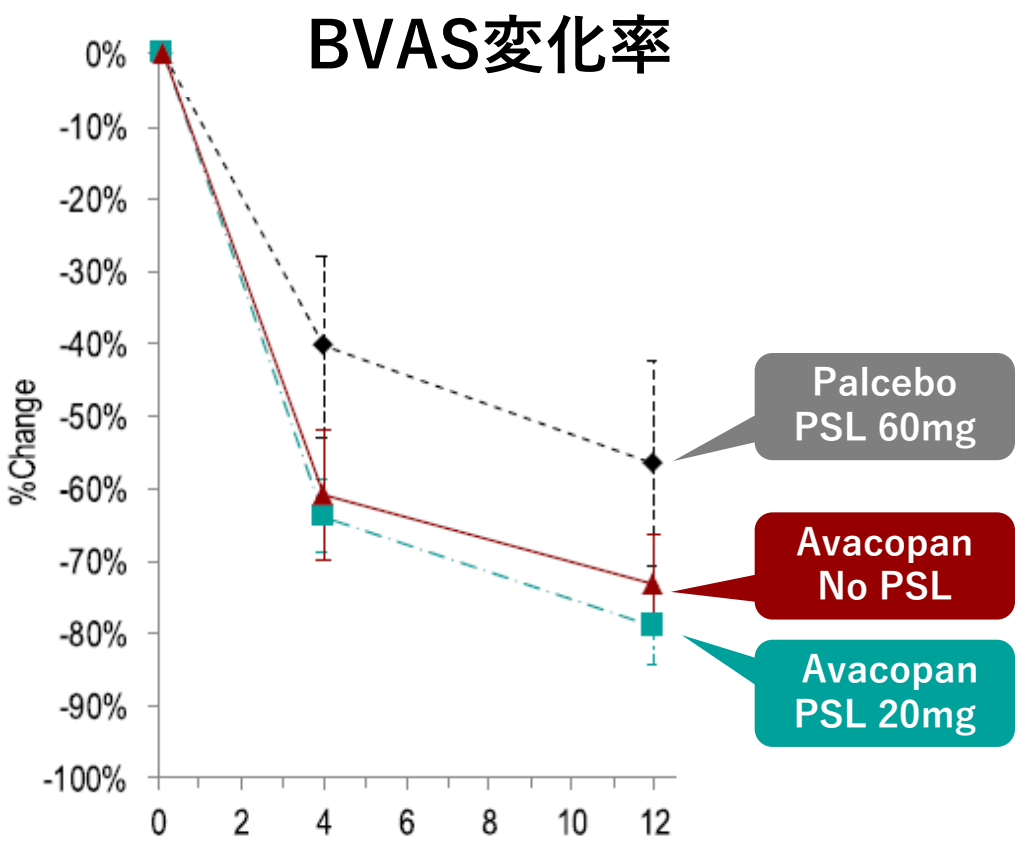
維持
Avacopan

# CLEAR (2017)

[J Am Soc Nephrol. 2017;28(9):2756-67.]

## Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

David R.W. Jayne,* Annette N. Bruchfeld,† Lorraine Harper,‡ Matthias Schaier,§ Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶ Michel Jadoul,** István Szombati,†† Vladimír Tesař,‡‡ Mårten Segelmark,§§ Antonia Potarca,‖‖ Thomas J. Schall,‖‖ and Pirow Bekker,‖‖ for the CLEAR Study Group



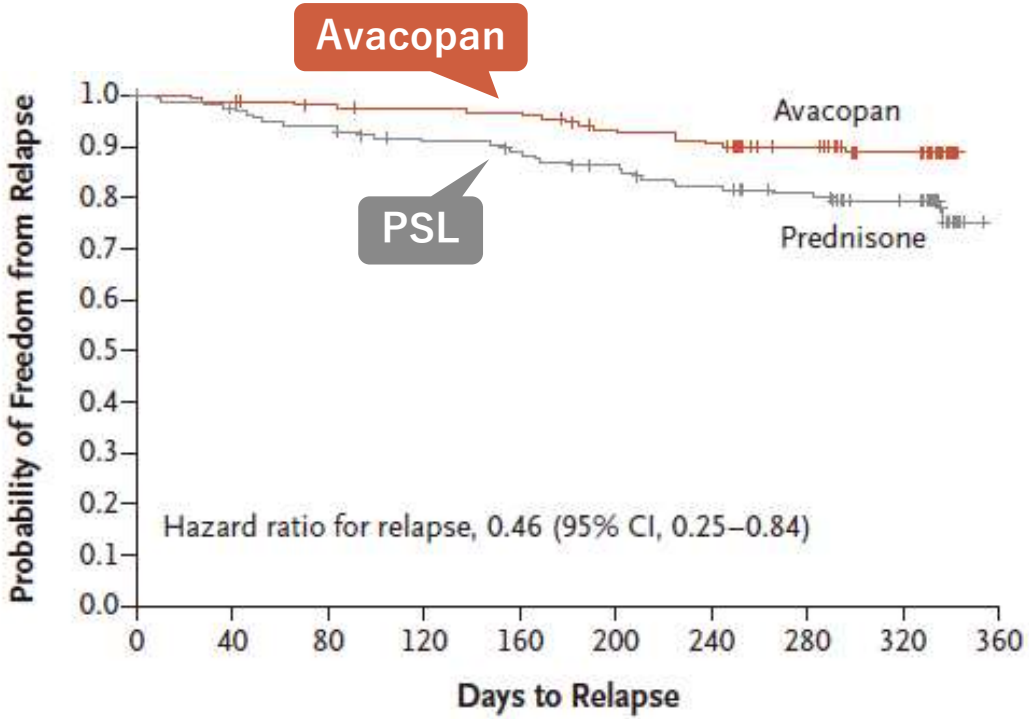

- Double blind, multicenter, RCT, 52w.
- Avacopan: C5aレセプター阻害薬, 内服薬
- 新規/再発AAV, IVCYかRTXで寛解→AZA維持, 3群割付
  - Placebo/PSL60mg群: 23人, PSL 2wから漸減21wでoff
  - Avacopan(30mg bid)/No PSL群: 22人
  - Avacopan/PSL20mg群: 22人, PSL漸減15wからoff
- Endpoint: CR [12w以内にBVAS<50%/臓器再発なし]
- 結果: 12週CR率に有意差あり；
  - Placebo/PSL60mg群: **70%**
  - Avacopan/NoPSL群: **81%** (p=0.01)
  - Avacopan/PSL20mg群: **86.4%** (p=0.002)
- 有害事象:
  - Placebo/PSL60mg群: **91%**
  - Avacopan/NoPSL群: **96%**
  - Avacopan/PSL20mg群: **86%**
- 結論: Avacopanは高用量PSLと代替可能な治療.

寛解導入
Avacopan

# ADVOCATE (2021)

[N Engl J Med. 2021;384(7):599-609.]

## Avacopan for the Treatment of ANCA-Associated Vasculitis




| Study Day | Avacopan Group | Prednisone Group | | | |
|---|---|---|---|---|---|
| | Daily Prednisone Dose* | | | | |
| | All† | Adults | | Adolescents | |
| | | ≥55 kg | <55 kg | >37 kg | ≤37 kg |
| Week 1 | 0 | 60 mg | 45 mg | 45 mg | 30 mg |
| Week 2 | 0 | 45 mg | 45 mg | 45 mg | 30 mg |
| Week 3 | 0 | 30 mg | 30 mg | 30 mg | 30 mg |
| Week 4 to 6 | 0 | 25 mg | 25 mg | 25 mg | 25 mg |
| Week 7 and 8 | 0 | 20 mg | 20 mg | 20 mg | 20 mg |
| Week 9 and 10 | 0 | 15 mg | 15 mg | 15 mg | 15 mg |
| Week 11 to 14 | 0 | 10 mg | 10 mg | 10 mg | 10 mg |
| Week 15 to 20 | 0 | 5 mg | 5 mg | 5 mg | 5 mg |
| ≥ Week 21 | 0 | 0 | 0 | 0 | 0 |

- Phase 3, 二重盲検RCT, 多施設共同 (20ヵ国143施設)
- Avacopan (30mg bid)をPSL (規定の漸減)と比較し有効性/安全性評価 (背景治療はIVCY→AZA or RTX).
- 1次endpoint: 26w 寛解 (26w BVAS 0 & 22w- PSL 0)
- 2次endpoint: 52w 寛解維持 (26w, 52wとも寛解)
- 新規/再発 GPA/MPA,MPO/PR3-ANCA+ 331人.

- Inclusion: eGFR>15, BVAS major>1 or minor>3 or 腎>2
- Exclusion: 人工呼吸要するDAH, 12w以内のPE/HD etc.
- Avacopan群 (166人): 26w寛解 72.3%, 52wも寛解 65.7%
- PSL群 (165人): 26w寛解 70.1%, 52wも寛解 54.9%
- 26w (非劣性 p<0.001, 優越性 p=0.24), 52w (非劣性 p<0.001, 優越性 p=0.007)
- Avacopan群はPSL量 1/3. eGFR改善率高い,
- 重篤な有害事象: Avacopan群 37.3%, PSL群 39.0%. 莢膜を持つ細菌感染症はなかった. 重篤な感染症はPSLが多い.
- 結論: Avacopanは26wの寛解ではPSLと非劣勢 (優越性なし), 52w寛解維持率はPSLより高い.

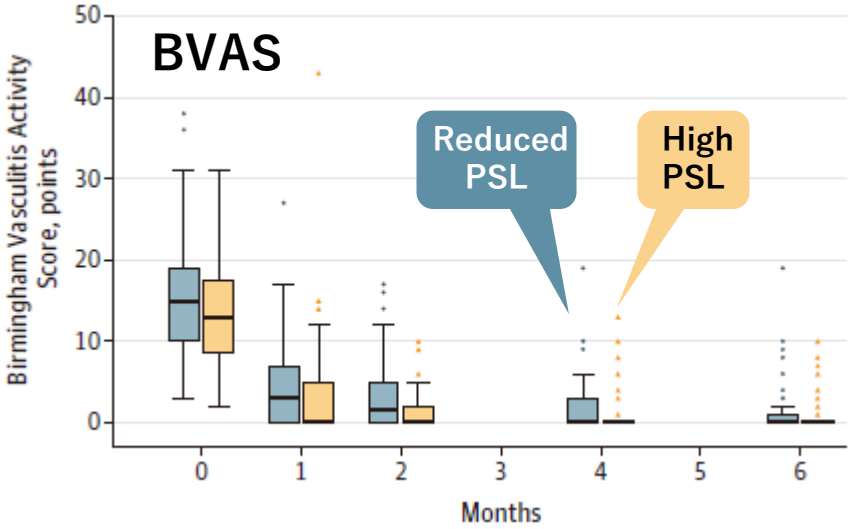
寛解導入
low/hi PSL

JAMA | Original Investigation

# Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis
A Randomized Clinical Trial

# LoVAS (2021)
[JAMA. 2021;325(21):2178-87.]

| Outcomes | Reduced-dose glucocorticoid plus rituximab (n = 69) No. (%) with data | Median (IQR) | High-dose glucocorticoid plus rituximab (n = 65) No. (%) with data | Median (IQR) | Absolute difference (95% CI) | P value[a] |
|---|---|---|---|---|---|---|
| Primary outcomes | | | | | | |
| Remission[b] | 49 (71.0) | | 45 (69.2) | | 1.8 (−13.7 to ∞)[c] | .003[d] |




## PSL減量Protocol

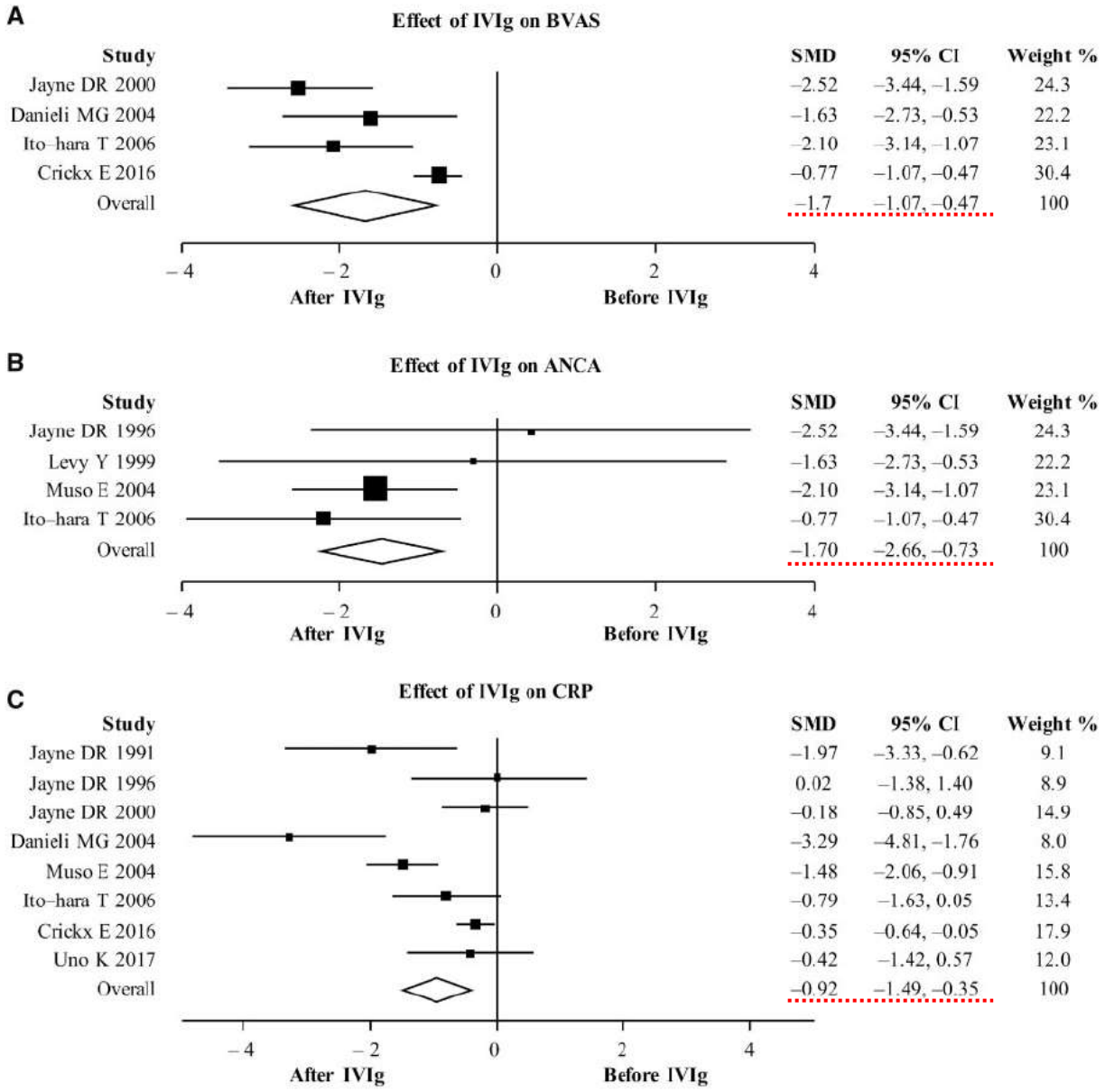
| Weeks | Reduced-dose regimen | High-dose regimen |
|---|---|---|
| 1-2 | 0.5mg/kg/day | 1.0mg/kg/day |
| 3-4 | 0.25mg/kg/day | 0.8mg/kg/day |
| 5-6 | 7.5mg/body/day | 0.7mg/kg/day |
| 7-8 | 5mg/body/day | 0.5mg/kg/day |
| 9-10 | 4mg/body/day | 0.4mg/kg/day |
| 11-12 | 3mg/body/day | 0.35mg/kg/day |
| 13-16 | 2mg/body/day | 15mg/body/day |
| 17-20 | 1mg/body/day | 12.5mg/body/day |
| 21-24 | 0mg/body/day | 10mg/body/day |

- Phase 4, Open-label, 非劣性RCT, 日本の21施設.
- Reduced-doseとHigh-dose PSL比較.
- 対象: 初発MPA/GPA, MPO/PR3-ANCA陽性患者. 平均74歳, BVAS 14
- 除外: eGFR<15, $O_2$>2LのDAH
- Reduced PSL群(n69): 0.5mg/kg+ RTX
- High PSL群(n65): 1.0mg/kg+ RTX
- Primary endpoint: 6カ月後の寛解率 (BVAS 0点+ PSL<10mg)
- 2nd endpoint: BVAS, 寛解までの期間

- 結果: Reduced PSL群はHigh PSL群と比較し6ヶ月後の寛解率は非劣性 ($P = 0.003$) . 再発・死亡に有意差なし.
- 重篤な有害事象 ($P = 0.02$), 重篤な感染症 ($P = 0.04$)はReduced群で少なかった.
- 結論: 新規AAVに対してPSL減量群はPSL高用量群に比べ(ともにRTX併用) 6ヶ月後の寛解率は非劣性.
- PSL減量群では重篤な有害事象/感染症/PSL関連副作用は少なかった.
- AAVの臨床試験で, PSL減量により重篤な有害事象が減少することを証明した初めての報告である.

# The therapeutic efficacy of intravenous immunoglobulin in anti-neutrophilic cytoplasmic antibody-associated vasculitis: a meta-analysis

[Rheumatology (Oxford). 2020;59(5):959-967.]




- IVIgのメタ解析
- Active AAVにIVIg加療をした220報中, IVIg前後の臨床データがありcriteriaを満たす9報をメタ解析 .
- IVIg 6か月後にBVAS (SMD [standardized mean difference] -1.7, *P*=0.0006), ANCA (SMD -1.7, *P*=0.0006), CRP (SMD -0.92, *P*=0.002)が有意に低下.
- 免疫抑制療法で調整されないsubgroup解析で, IVIg半月後にBVAS (SMD -1.39, *P*=0.003), CRP (SMD -0.56, *P*=0.002)は有意に低下.
- 結論: IVIgはactive AAV患者の疾患活動性(BVAS), ANCA, CRPを低下させうる.
- 治療効果はおよそ半月以内に認める.