Remission: The Facts, What is Possible

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Ulrich Specks, M.D.
Connor Group Foundation Professor of Medicine
Mayo Clinic College of Medicine & Sciences
Chair, Division of Pulmonary & Critical Care Medicine
Mayo Clinic, Rochester, MN

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Concepts apply to vasculitis in general
Specifics apply mostly to GPA and MPA

What does “Remission” mean?

- What does it mean for you (patients)?
- What does it mean for me (physicians)?
- How can we assure we talk about the same thing and the same goals?

Definitions of "Remission"
Ask Dr. Google

- Merriam-Webster: (fairly useless)

- Wikipedia: "**Remission** is either the reduction or disappearance of the signs and symptoms of a disease. The term may also be used to refer to the period during which this diminution occurs. A **remission** may be considered a partial **remission** or a complete **remission**."

- MedicineNet: "**Remission**: Disappearance of the signs and symptoms of cancer or other disease. A **remission** can be temporary or permanent"

General Implications:
- The disease is chronic (no cure [yet])
- The disease may act up again (relapse)
- Something needs to be done to maintain the state of remission
  - ✓ as long as possible,
  - ✓ ideally forever

What does “Remission” mean?

- Surviving the disease is the first condition
- Remission – the goal of treatment
  - It needs to be induced
  - It needs to be maintained
- What “remission” means to physicians:
  - Absence of disease activity = measurable inflammation
- “Remission” does not necessarily mean “absence of symptoms” or “feeling normal”
- Damage causes symptoms & needs to be prevented
- “Feeling normal” is ultimate goal

“Remission” as Clinical Trial Outcomes Measure

Example: RAVE Efficacy Outcomes (independent of 6 months time point)

BVAS/WG = 0 means no measurable inflammatory activity (disease activity)

	RTX (N=99)	CYC/AZA (N=98)	*P*
Complete remission (BVAS/WG=0 & Pred = 0 mg) at any time	76 (77%)	70 (71%)	*0.15*
BVAS/WG=0 & Pred<10 mg at any time	82 (83%)	84 (86%)	*0.91*
Remission (BVAS/WG=0) at any time	89 (90%)	89 (91%)	*0.50*

Specks et al. NEJM 2013; 369:417-27

Keys to Better Outcomes (Improved Survival)

- Early diagnosis
- Effective drugs (GCS, RTX, CYC)
- Preservation of renal function
- Prevention of serious infections
  - Less glucocorticoids
  - Prophylaxis

Remission Maintenance – WHY?

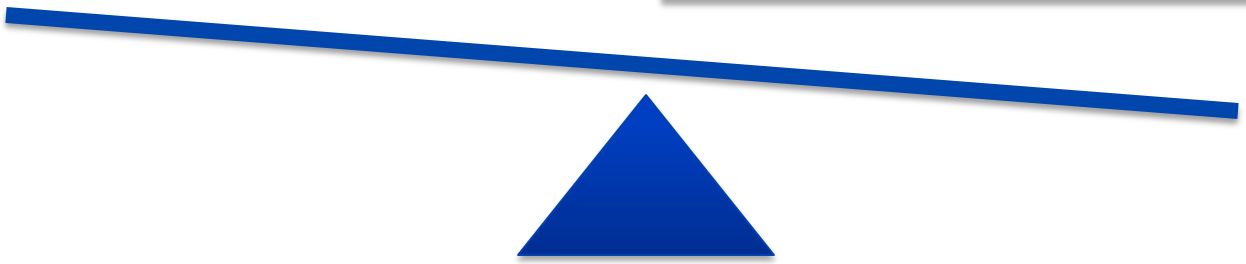
- Ideally, to have you feel normal forever

➢ Minimize “damage” = irreversible loss of organ function

Ultimate Management Dilemma in ANCA-associated Vasculitis

Risk of Relapse
Cumulative Damage
Cumulative Steroid Exposure

Risk of Preventive Therapy
Efficacy of Maintenance
Toxicity of Maintenance
Cumulative Cyclophosphamide Dose



MAYO CLINIC

Tervaert JW. Lancet 1990;336(8717)709-11.
Kerr GS.Arthritis Rheum 1993;36(3):365-71.

Ultimate Management Dilemma in ANCA-associated Vasculitis

What is the Balance Today?

Rituximab

?

Remission Maintenance – HOW?

- Remission maintenance needs to be individualized
  - Who needs maintenance therapy?
  - How to monitor (which) patients in remission?
  - Which drugs to use for which patient
  - For how long should maintenance therapy be continued?
- What we know, we know from clinical trials:
  - Efficacy and toxicities of drugs
  - Defined groups of patients

Remission Maintenance – HOW?

Who needs maintenance therapy?

Remission Maintenance – HOW?
Monitoring during remission – the Six Pack

- Sedimentation rate, C-reactive protein
- Complete blood count with differential
- Metabolic panel (kidney and liver function)
- Urinalysis
- Chest imaging
- ANCA

Look for return of disease activity and for treatment side effects

RTX versus AZA for Remission Maintenance in AAV MAINRITSAN Trial

Induced with CYC (n=115)

Primary Endpoint:

Relapse rate at 28 mo

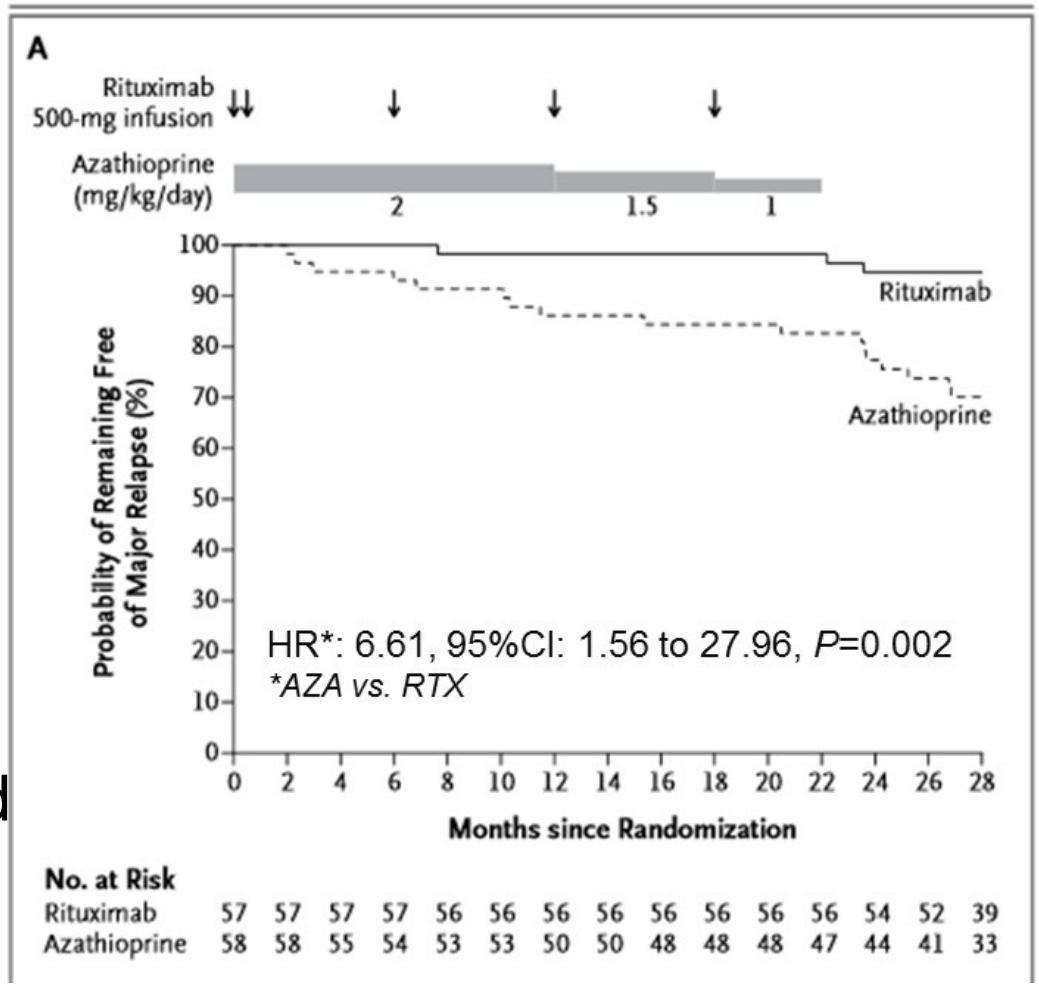
Results:

Pts (%) with major relapse

AZA: 17 (29%)

RTX: 3 (5%)

To avoid 1 event, 4 pts had to be treated with RTX.



Guillevin et al. NEJM 2014;371:1771-1780.

RTX versus AZA for Remission Maintenance in AAV MAINRITSAN Trial

Economic Evaluation

	Azathioprine		Rituximab	
	Mean(SD)	Median[IQR]	Mean(SD)	Median[IQR]
Inpatient stays, n	1.9(2.6)	1[0–2]	1.7(2.9)	1[0–2]
Length of stay (days)	14.1(24.1)	7[1–16]	12.1(13.6)	7[5–14]
Outpatient visits, n	3.5(4.9)	1[0–5]	6.3(2.8)	6[5–7]
Cost (€/patient)				
Protocol drug	313(130)	337[(264–391]	6,035(165)	6,057[6,057–6,057]
Its administration	0	0[0–0]	2,467(1,076)	2,020[1,830–2,875]
Maintenance therapy	633(1,808)	0[0–0]	0(0)	0[0–0]
Relapses	2,547(4,748)	0[0–4,737]	724(3,537)	0[0–0]
Side effects	2,606(6,622)	0[0–2,523]	1,983(4,908)	0[0–2,531]
Follow-up	2,954(5,611)	636[0–3,254]	1,713(3,809)	0[0–2,426]
Outpatient visits	993(407)	1,069[770–1,314]	748(285)	615[614–669]
Total cost	**10,046**(10,558)	6,049[2,140–14,501]	**13,67**(7,946)	10,942[9,103–14,197]

Rituximab was cost effective:

- Higher drug costs offset by higher relapse rate and renal damage
- Incremental cost effectiveness ratio: 259 Euro/avoided relapse

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Montante et al. Rheumatology 2017;March:iii32-3.

RTX versus AZA for Remission Maintenance in AAV
RITAZAREM Trial (n=190)

Induction with RTX

All Relapsers (severe or non-severe)

Randomized at 4 mo (n=160)

2 Glucocorticoid dosing options

Intervention:

1g of RTX q 4 mo *vs* daily p.o. AZA

Primary Endpoint:

Time to relapse at 24 mo

Results:

Enrollment completed

Primary outcome results pending

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Gopaluni et al. Trials 2017; 18 (1):112.

Opportunities to Improve Remission Maintenance

Can retreatment be individualized?

The search for biomarkers

- Listen to the patient
- ANCA?
- Other biomarkers?

Can retreatment be individualized?

The PGA as a biomarker?

The Value of a Patient Global Assessment of Disease Activity in Granulomatosis With Polyangiitis (Wegener's)

Table 3. Patient global assessment scores during times of remission and disease relapse*

	Score	*P*†
Remission (n = 885)‡	15.7	Referent
Two visits prior to relapse (n = 70)	17.7	0.41
One visit prior to relapse (n = 103)	20.2	0.03
Relapse visit (n = 103)	28.2	<0.001

* Values are the mean patient global assessment scores (n = number of study visits) during remission, at visits leading up to disease relapse, and at visits after disease relapse.
† Versus the referent group.
‡ Remission that is not followed by a relapse during the next 2 study visits.

Tomasson et al. Arthritis Rheum 2014; 66:328-32.

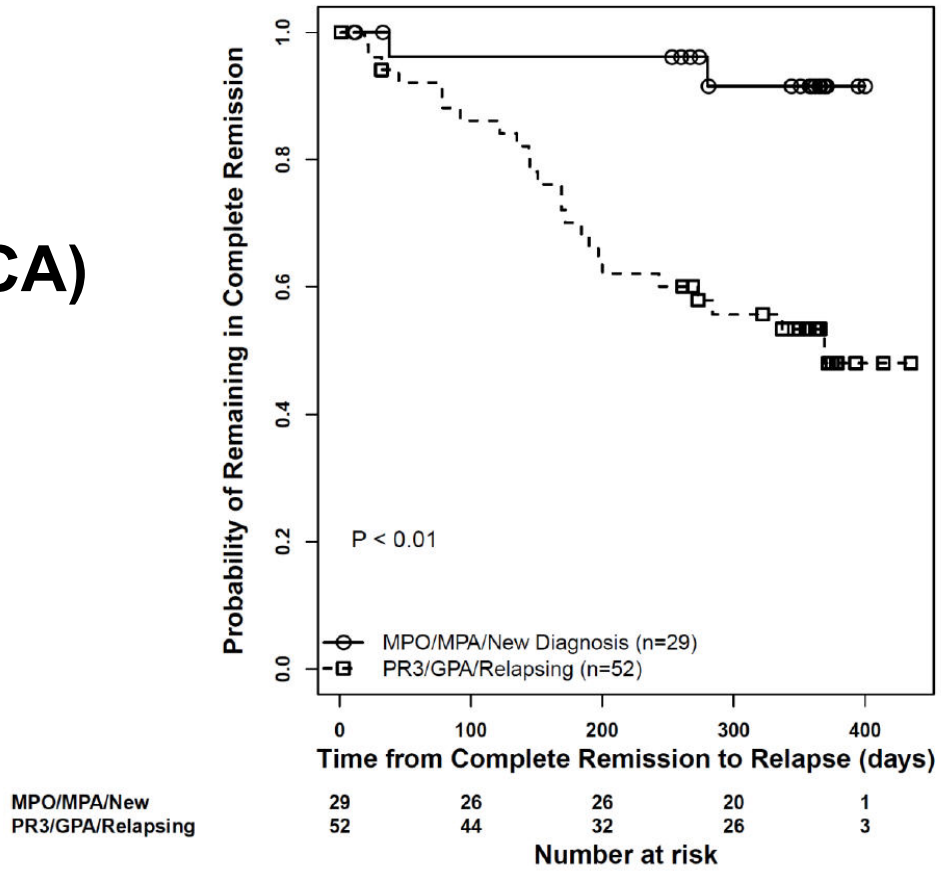
Opportunities to Improve Remission Maintenance

Who needs remission maintenance?

Long-term RAVE data by Disease Phenotype

Factors associated with high relapse rate:

- **GPA (vs MPA)**
- **PR3-ANCA (vs MPO-ANCA)**
- **Having had a relapse**



Can retreatment be individualized?
Serial PR3-ANCA Testing

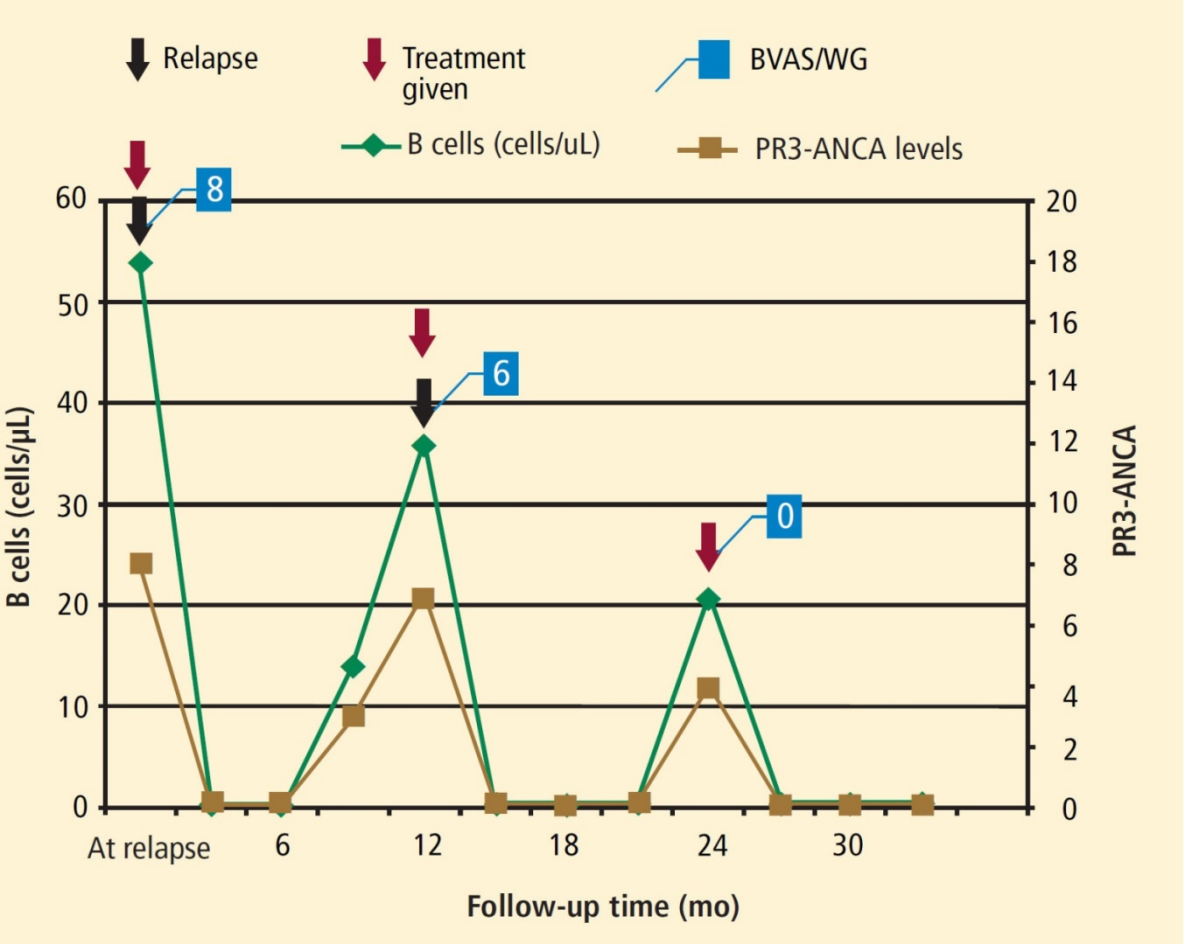
Factors determining clinical utility for relapse prediction analyzed in RAVE trial

Risk of relapse following PR3-ANCA rise depends on:

- Assay methodology: most sensitive not best
  - Know thy assay
  - Use same assay serially
- Disease phenotype at baseline:
  - Most useful in patients where disease manifestations attributable to capillaritis dominate the clinical presentation
- Patient's treatment
  - Most useful following rituximab therapy

Can retreatment be individualized?

Individualized RTX retreatment based on B-cells & PR3-ANCA



MAINRITSAN II Trial:

- same efficacy
- fewer RTX infusions
- same AEs
- ANCA not helpful

ANCA workshop Tokyo 3/17

Specks U. CCJM 2012; 79 (Suppl 3):S50-53.
Cartin-Ceba et al. Arthritis Rheum 2012; 64:3770-8.

Summary: what have we learned

- Different patients have different relapse risk
  - Example: PR3-ANCA (high), MPO-ANCA (low)
- The individual need to prevent the next relapse varies
  - Example: Patient with CKD 3-4 (high), normal kidneys (low)
- We know something about the efficacy of different drugs
  - Example: AZA, MTX, MMF are similar, RTX is better
- Patients need to be monitored during remission for:
  - Stability of remission
  - Toxicity of medications (prevent them as best as possible)
- The specific remission maintenance and monitoring regimen needs to be determined individually between each patient and their “vasculitis quarterback”.

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  - **PATIENTS and their loved ones!**

