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Remission: The Facts, What is Possible

Ulrich Specks, MD

Mayo Clinic, Rochester, Minnesota

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Note: These are just some of the slides from the original presentation.

The full video version of this lecture with all of the slides will be featured on the VF Website in September 2019.

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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- Off-label use:

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?

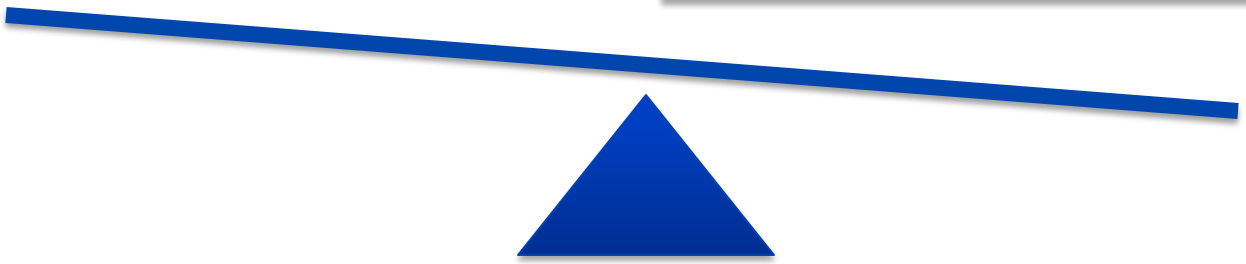
- Ideally, to have you feel normal forever

➢ 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



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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

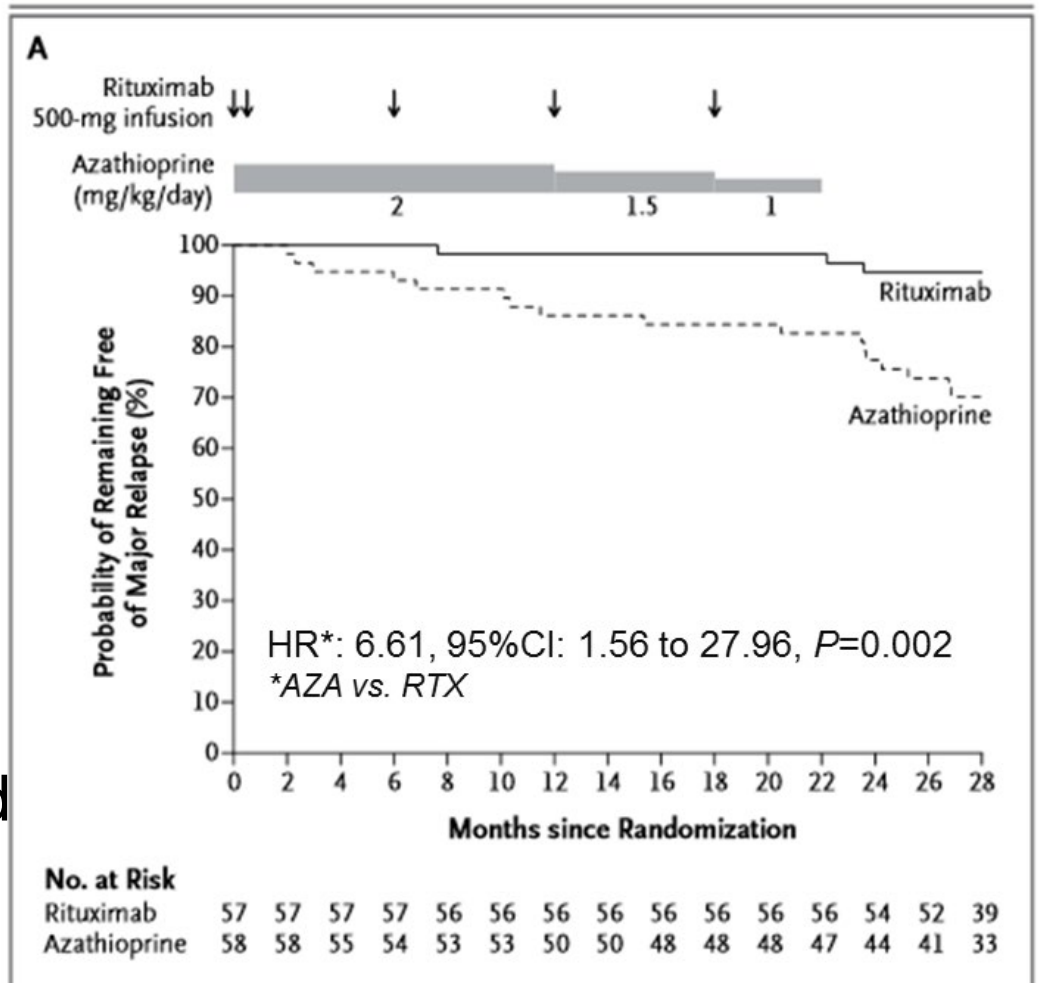
Results:

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.

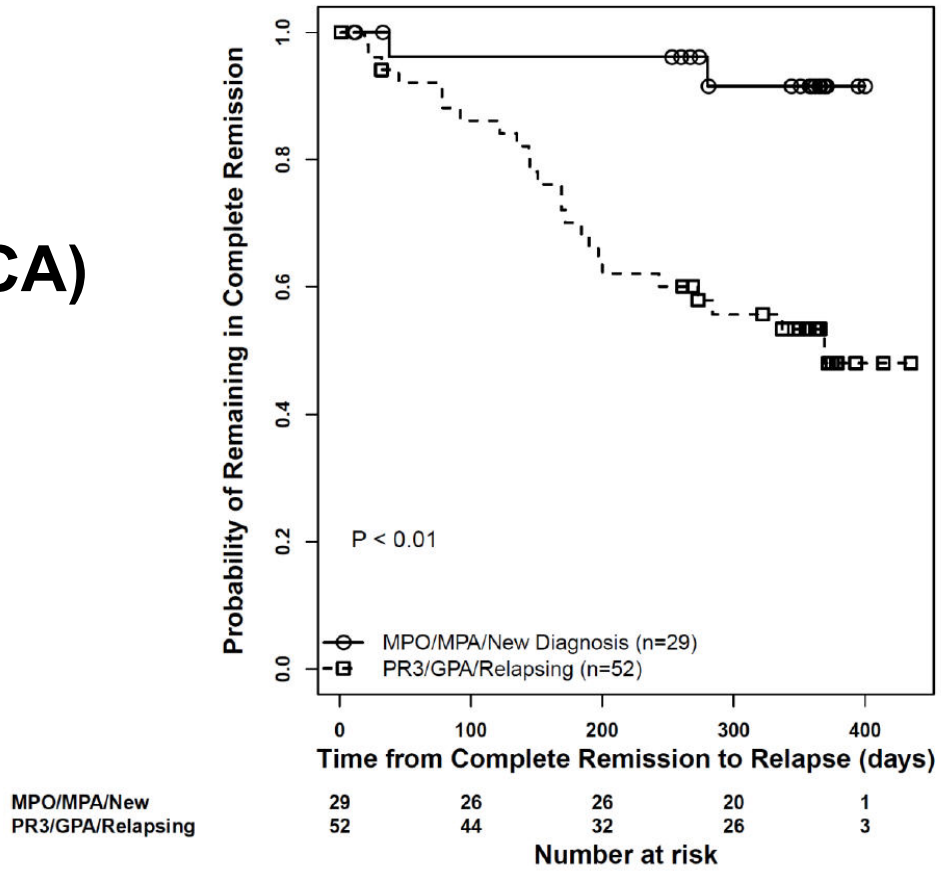
Opportunities to Improve Remission Maintenance

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

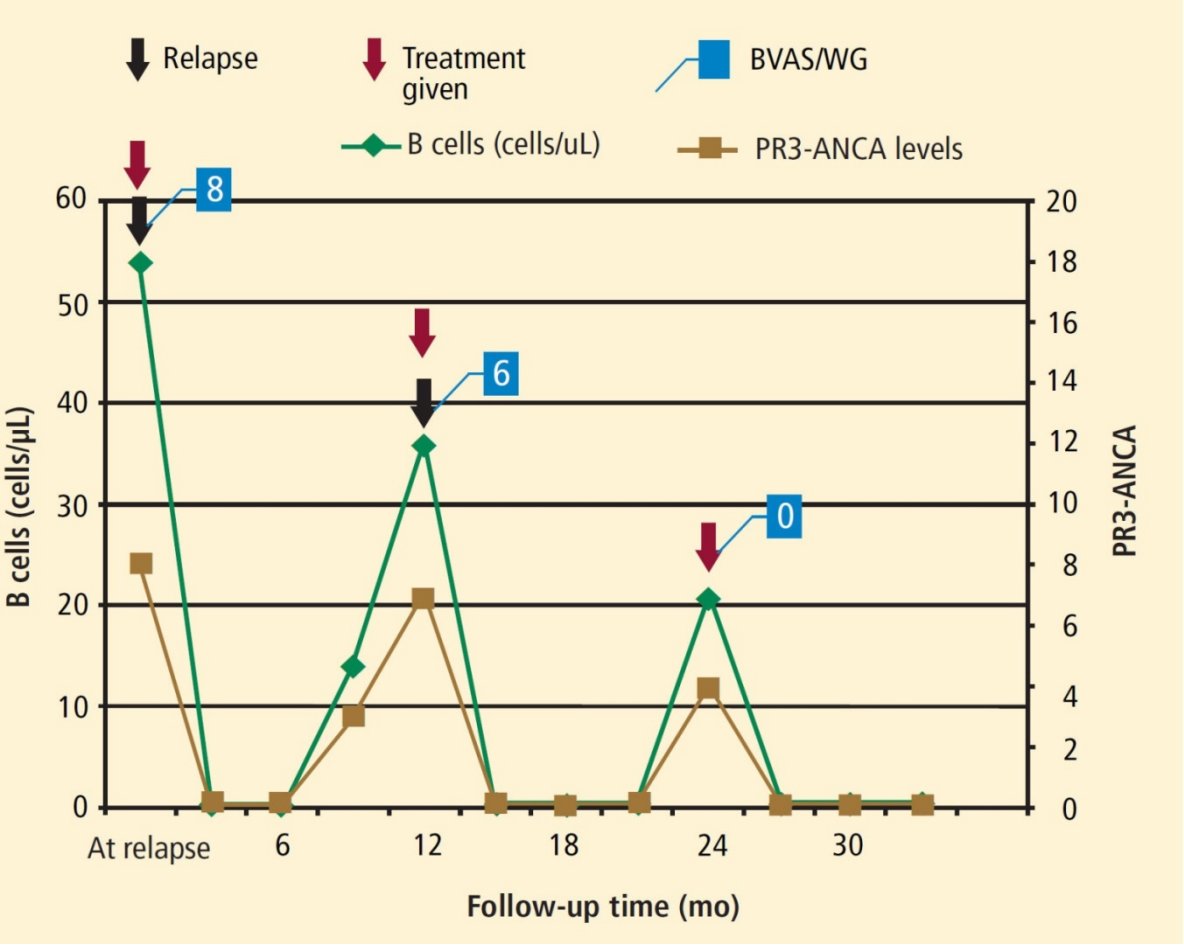
Factors determining clinical utility for relapse prediction analyzed in RAVE trial

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”.

Acknowledgements

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  - **PATIENTS and their loved ones!**

