Autoimmune Bullous Disease: Pemphigus

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Conflict of Interest

- PI, Dapsone trial for pemphigus (no funding)
- Desmoglein-3 synthetic peptide (PI-0824) (Peptimmune)
- P38 MAPK inhibitor (Kemia)
- Infliximab Trial (PI: Russ Hall, NIAID)
- VAY (Novartis, anti-BAFF receptor)
- Rituximab (Roche, Genentech)

Conflict of Interest

- Syntimmune (monoclonal antibody against FcRn receptor)
- Helped develop the Pemphigus Disease Area and Severity Index (PDAI)
- Medical Advisory Board, International Pemphigus and Pemphigoid Foundation (IPPF)
- Consultant: Novartis, Lilly, Immune Pharma, Pharmacia

Rituximab: A New Treatment Option in PV

- Rituximab, a CD20-targeting monoclonal antibody, is a treatment option for many autoimmune diseases
  - Targets CD20-expressing B cells
- Safety and efficacy in severe PV demonstrated in ≈500 patients across several small trials and case studies, with clinical remission occurring within 6 wks in up to 95% of patients[1]

US FDA, United States Federal Drug Administration

1. Ahmed AR, Shetty S. *Autoimmun Rev.* 2015;14(4):323-331.

Anti-CD20 (Rituximab)

- **Improvement with combined anti-CD20 and IVIG *(Ahmed et al, NEJM 355:1772, 2006)***
- **86% of patients (18/21) responded to one course of 4 weekly infusions of Rituximab *(Joly et al, NEJM 357:545, 2007)***
- **Controlled trials ongoing in Europe (Joly)**

Joly P et al, Lancet 389:2031-2040, 2017

Rituximab

- **French study, 91 patients (74 with PV)**
- **Participants (1:1) received either oral prednisone alone, 1·0 or 1·5 mg/kg per day tapered over 12 or 18 months (prednisone alone group)**
- **or 1000 mg of intravenous rituximab on days 0 and 14, and 500 mg at months 12 and 18, combined with a short-term prednisone regimen, 0·5 or 1·0 mg/kg per day tapered over 3 or 6 months (rituximab plus short-term prednisone group).**
- **Follow-up was for 3 years**

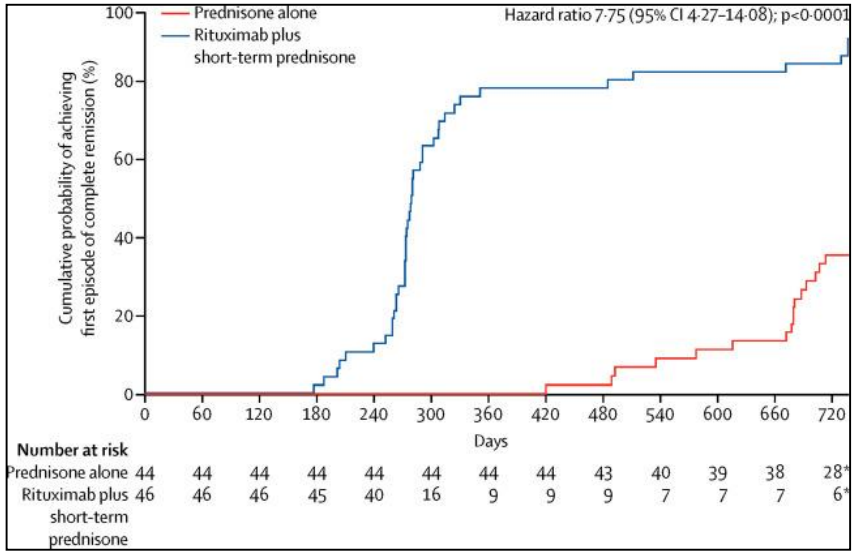
Rituximab

- **At month 24, 41 (89%) of 46 patients assigned to rituximab plus short-term prednisone were in complete remission off-therapy versus 15 (34%) of 44 assigned to prednisone alone (absolute difference 55 percentage points, p<0·0001.**

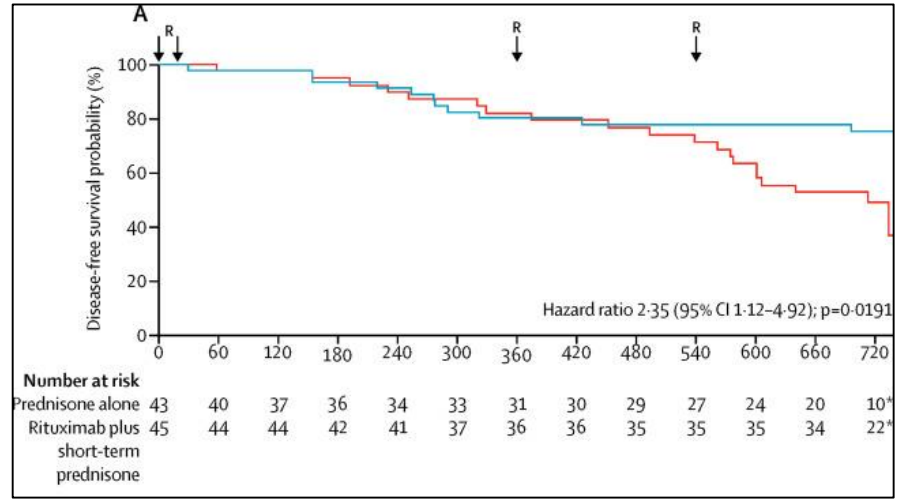
Joly P et al, Lancet 389:2031-2040, 2017

Phase 2 Trial: Rituximab Improves Outcomes

24-mo remission rate: 89% vs 34%



Disease-free survival at 24 mo: 75.4% vs 36.7%



Safety

- No treatment-related deaths
- Fewer severe grade 3/4 treatment-related adverse events in rituximab arm

Joly P, et al. *Lancet.* 2017;389:2031-2040.

Rituximab

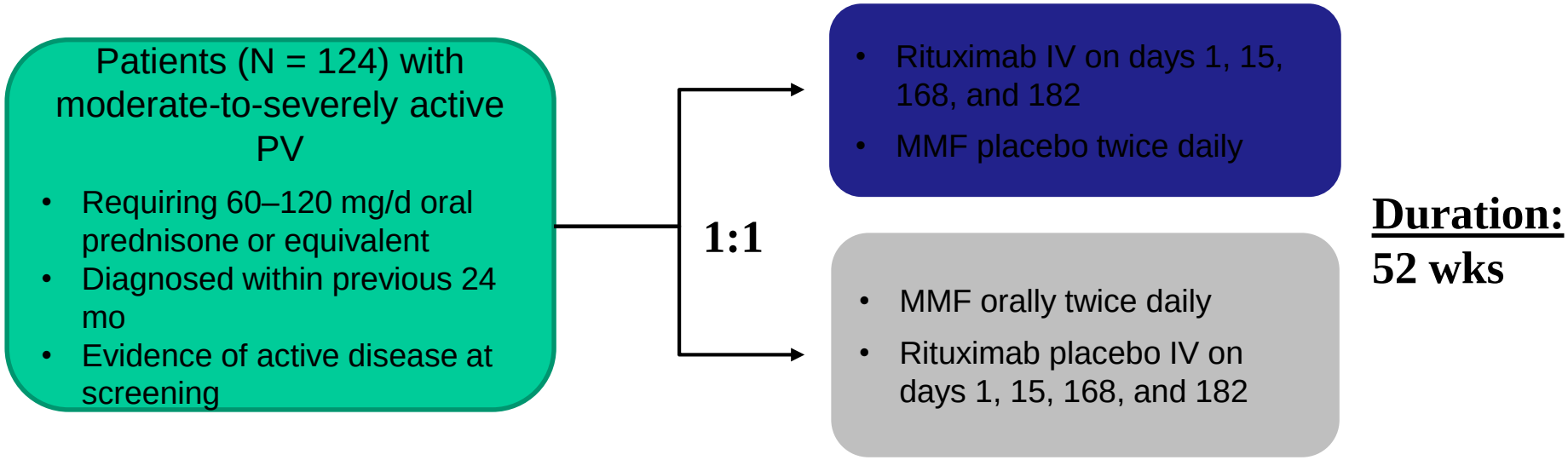
- Has changed treatment of pemphigus
- Given either 375 mg/m^2 every week x4 or 1000 mg every other week X2.
- Relapses frequent, average about 18 months but early relapses also occur
- May need to retreat at six months if still active or consider retreatment between 6 and 12 months to prevent relapse
- Need more data to know optimal management with Rituximab

Treatment Considerations with Rituximab

- Infusion reactions
- Hepatitis B Virus Reactivation: Have to check for Hep B surface antigen and Hep B core antibody
- Progressive multifocal leukoenceophalopathy: JC virus (rare, not seen in pemphigus yet)
- Chills, infections, body aches, tiredness, low WBC, more URI's

Phase 3 PEMPHIX Trial

A phase 3, randomized, double-blind, double-dummy, active-comparator, parallel-arm, multicenter study currently ongoing



Primary Endpoint: Percentage of participants who achieve sustained complete remission as evaluated by PDAI (from baseline up to 52 wks)

Key Secondary Endpoints: Time to and duration of complete remission, time to and number of protocol defined disease flares, change in health-related QoL, adverse events, change in PV disease scores

Current Rituximab Use

- Granted Breakthrough Therapy designation by US FDA for treatment of PV in March 2017
- Priority Review by FDA in February 2018
- US regulatory approval expected in mid-to-late 2018

US FDA, United States Food and Drug Administration

Harman KE, et al. *Br J Dermatol.* 2017;177:1170-1201.

Treatment Considerations

- Rituximab rapidly becoming first line therapy
- Early evidence of potential clinical benefit in serious disease to help ensure patients receive access to medicines as soon as possible
- Phase III study: PEMPHIX - finished enrolling and should have data shortly