Rituximab in ANCA-associated vasculitis: a revolution?

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On 19 April 2011, the US Food and Drug Administration (FDA) approved rituximab in combination with glucocorticosteroids for the treatment of two forms of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV): granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis. Rituximab is the first FDA approved drug for ANCA-associated vasculitis. It is to be expected that also the European Medicines Agency (EMEA) will approve rituximab in the next coming years. Patients and doctors applaud for the approval of this drug: there is hope that rituximab will replace in the future the current standard therapy with cyclophosphamide.

Rituximab is a generic monoclonal anti-CD20 antibody that selectively depletes B lymphocytes but no plasma cells. It is licensed for B-cell lymphoma and rheumatoid arthritis. Since the discovery of ANCA in granulomatosis with polyangiitis (Wegener’s), microscopic polyangiitis and the Churg–Strauss Syndrome intensive studies have been performed to demonstrate the pathogenesis of ANCA in small vessel vasculitis [1]. Initially, most studies were performed on myeloperoxidase (MPO)–ANCA in rats demonstrating that MPO–ANCA alone is sufficient to cause disease [2–4]. In crucial experiments performed in MPO knockout mice that were immunized with mouse MPO, it was demonstrated that the transfer of MPO–ANCA could induce a mild form of vasculitis [5]. Additionally, Huugen et al. [6] demonstrated that a full-blown form of vasculitis developed when MPO–ANCA was transferred in combination with LPS. For the other form of ANCA that is specific for small vessel vasculitis, i.e. proteinase 3 (PR3)-ANCA, it has been much more difficult than for MPO–ANCA to demonstrate pathogenicity in animal models. Only in 2010, Primo et al. [7] demonstrated the transfer of splenocytes from PR3-immunized non-obese diabetic (NOD) mice into immunodeficient NOD mice-induced glomerulonephritis. More recently, Little et al. [8] reported during the 15th International Vasculitis and ANCA Workshop in Chapel Hill, USA, that mice with a humanized immune system could develop severe pulmonary and renal vasculitis after infusion of human PR3-ANCA in combination with LPS. So, although ANCA is sufficient to cause disease in animal models, it is clear that additional environmental factors may amplify the disease phenotype. Important environmental factors are silica and infections [9, 10]. Especially in PR3-ANCA-associated vasculitis, it has been hypothesized that Staphylococcus aureus plays a pivotal role [11]. Not only the antibody plays a pivotal role in disease pathogenesis but also the antigen is crucial. Recently, the group of Ron Falk demonstrated that epigenetic control of the antigen is disturbed in patients with AAV [12].

Since AAV is induced by ANCA, the rationale for rituximab to deplete CD20+ precursors of ANCA-secreting plasma cells was logical. B cells, however, are not only precursors of plasma cells: they have also other pathophysiological roles in AAV. Importantly, it has been demonstrated that activated B cells closely correlate with the disease activity [13]. Furthermore, autoantigen-specific B cells are present at sites of inflammation where tertiary lymphoid-like organs are formed [14]. B cells may produce pro-inflammatory cytokines and may present antigens to T cells. Importantly, it was recently demonstrated that rituximab also induces changes in T-cell populations, e.g., T helper 17 cells, that are relevant for AAV pathogenesis [15, 16]. These possibilities provided the basis for the hypothesis that rituximab therapy may be effective in AAV.

Cyclophosphamide has been used since the 1960s to treat AAV and this alkylating agent has been considered the best drug for this severe disease. Currently, the standard therapy consists in cyclophosphamide intake, either orally or intravenously, for 3–6 months and then subsequently maintenance therapy with azathioprine. Furthermore, there is evidence that plasma exchange is beneficial in severe cases of vasculitis and possibly also in moderate severe cases. Despite this current therapy, the outcome of AAV is poor. Mortality is still 15–25% after 2 years and at least 20% of survivors of ANCA-associated renal vasculitis develop end-stage renal disease. Survivors have markedly increased rates of cardiovascular disease and have an increased rate of developing malignancies. Furthermore, AAV is a relapsing disease in which patients with PR3-ANCA experience 0.20 relapses per patient per year. Although relapse rates in MPO–ANCA are substantially
Currently first choice therapy. The dosage of rituximab given and/or are intolerant to standard therapy), rituximab is cur-
relevent angiitis. This is not only true for patients with a renal
comparative efficacy compared with the restart of therapy with cyclo-
study versus 2 of 11 (18%) cyclophosphamide-treated pa-
rates. At six months, 64% of those who received rituximab
reported [19, 20]. At 2 years follow-up, relapse occurred
despite the absence of any maintenance therapy in only 7
of 33 (21%) rituximab-treated patients in the RITUXVAS study
versus 2 of 11 (18%) cyclophosphamide-treated patients,
who where on maintenance therapy with azathioprine
during these 2 years. After 18 months follow-up in the RAVE study, 36% of the patients in the rituximab arm were
still in remission without any drugs versus 31% of the patients
who received cyclophosphamide and maintenance azathioprine.
The number of flares did not differ between treatment arms. From these RCT’s, it can be concluded that
rituximab in newly diagnosed AAV is an effective alternative
for cyclophosphamide, especially when cyclophos-
phosphate cannot be used because of, for instance, a high risk of
infertility and/or malignancy.

From the RAVE trial, it is suggested that relapsing
patients have a better response to rituximab treatment when
compared with the restart of therapy with cyclophos-
phamide [18]. This is not only true for patients with a renal
relapse but also for patients with retro-orbital granulomata
and/or severe pulmonary and/or ENT relapses. Further-
more, in patients with refractory disease (those who do
not respond to standard therapy, have frequent relapses
and/or are intolerant to standard therapy), rituximab is cur-
rently first choice therapy. The dosage of rituximab given
in these cases is either 375 mg/m²/week for 4 weeks or two
infusions of 1000 mg each given 2 weeks apart.

A major question still is whether rituximab should be
combined with cyclophosphamide for induction therapy.
In the RITUXVAS trial, two doses of cyclophosphamide
(15 mg/kg) were additionally given with the first course of rituximab [17]. In the RAVE trial, however, no cyclophos-
phamide was added to rituximab [18].

In the current issue of Nephrology, Dialysis, Transplan-
tation, Mansfield et al. [19] report their experience with
rituximab in patients with moderately severe renal AAV. In
their protocol, patients received next to rituximab intra-
venous cyclophosphamide with two doses of 10 mg/kg
(maximum 750 mg) and subsequently four doses of 500
mg (or 10 mg/kg if < 50 kg bodyweight). Induction of
remission with this combination of cyclophosphamide and
rituximab was successful in all patients. It remains to be
seen, however, whether concomitant cyclophosphamide
was really needed in these patients. At present, I propose
that cyclophosphamide may be added when the patient has
severe and/or life threatening AAV and that cyclophos-
mide is not needed in less severe forms of AAV. In both the
RITUXVAS and RAVE study, no maintenance therapy was
given. Since a substantial amount of patients will relapse
(vide supra), most patients will need additional therapy in
the future. Several approaches can be used (i) re-treatment
with rituximab when a relapse occurs, (ii) prevention of
relapses by using maintenance therapy with immunosuppres-
sive such as azathioprine, mycophenolate mofetil and/or
methotrexate and (iii) prevention of relapses with rituximab.
During the 15th ANCA Workshop, the Cambridge group
reported their experience with protocolized re-treatment of
rituximab [22]. When rituximab was given every 6 months
(1 g after initial dose of 2 × 1 g), 22% (11 of 49 patients)
relapsed. In the study by Niles et al. [23], continuous B-cell
depletion with rituximab every 4 months was used resulting
in only nine relapses in 72 patients. Although these studies
are all rather small, they point out that maintenance therapy
with rituximab may be an option to control the disease.
Another interesting approach has been used in the Mayo
Clinics where timing of re-treatment with rituximab was
based on B-cell counts and ANCA levels. Pre-emptive ther-
apy of rituximab resulted in persistence of remission in all
their patients (N = 138 courses of rituximab [24]).

In the study by Mansfield et al. [21], patients received
maintenance therapy with azathioprine to prevent relapses.
At a medium follow-up of 30 months, 5 of 23 patients had a
relapse which could be treated with re-dosing with ritux-
imab. In four of five patients, B cells were repopulated
and ANCA titers rose before the relapse was diagnosed.
The fifth patient did not have an ANCA rise and had minor
symptoms (only arthralgias) that disappeared with a short
course of corticosteroids. Based on their experience, Mans-
field et al. conclude that their study protocol provided a
therapeutic regimen that was effective both for induction
and for prevention of relapses. The prevention of relapses,
however, should be tested in a RCT in which re-treatment
with rituximab is compared with maintenance therapy with
azathioprine. This RCT is currently on going (maintenance
of remission using rituximab in systemic ANCA-associated
vasculitis = MAINRITSAN) (Clinical Trials. Gov inden-
tifier NCT 00748644).

At present, patients with newly developed AAV who are
going to be treated with rituximab should not yet receive
maintenance therapy. A tailor-made solution could be that
only those patients with a high-risk profile to relapse, i.e.,
patients who are PR3-ANCA positive, have extensive ENT
disease, and are nasal carriers of S. aureus will need main-
tenance therapy, either azathioprine or re-treatment with
rituximab.

At present, an important unsolved issue is that during
rituximab therapy adverse effects were frequently observed
[17, 18]. This is probably due to the high-dose steroids that
were used to treat these patients. Approaches to limit
corticosteroids should be studied and include induction
therapy with plasma exchange [25] or additional therapy
with anti-tumour necrosis factor blockers [26]. At present,
reduction of initial corticosteroid therapy seems to be the
most important issue for the research agenda. A major
concern of rituximab therapy in AAV is the occurrence
of infections especially when hypogammaglobulinemia occurs. Opportunistic infections such as progressive multifocal leukoencephalopathy due to JC virus are feared. Fortunately, until now, JC reactivation has not been described in AAV patients treated with rituximab, although it has been reported in systemic lupus erythematosus patients using rituximab.

Other rituximab-related side effects include infusion-related reactions and the development of human chimaera antibodies which potentially limit effectiveness of rituximab. Finally, rituximab-induced neutropaenia may occur.

In summary, rituximab is a revolution for the care of patients with AAV. Remarkably, already decades ago, it was suggested to deplete B cells in AAV with cyclophosphamide [27] and cyclophosphamide appeared to be an extremely powerful pre-emptive therapy after ANCA rises [28]. So, it is expected that B-cell depleting therapy with cyclophosphamide will be nearly completely replaced by rituximab and/or other B-cell modulating therapy [29] in the nearby future as therapeutic option for patients with AAV.

Conflict of interest statement. None declared.

(See related article by Mansfield et al. Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis. Nephrol Dial Transplant 2011; 26: 3280–3286.)

References