Seven clinical conundrums in the treatment of ANCA-associated vasculitis

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ABSTRACT

Granulomatosis with polyangiitis and microscopic polyangiitis are two autoimmune diseases characterised by necrotising small-vessel vasculitis and presence of antineutrophil cytoplasm autoantibodies (ANCA). Current immunosuppressive regimes that combine cyclophosphamide and glucocorticoids have dramatically improved the outcome for these patients. However, these treatments are associated with toxic effects and do not lead to permanent remission in the majority of cases. Newer approaches have been sought during the last 15 years, with improvement in medication protocols and inclusion of novel therapies. This review develops on seven clinical conundrums of evidence-based therapeutic strategies for ANCA-vasculitis, posed as questions on aspects such as the role of established drugs in both remission induction and maintenance: glucocorticoids (and its duration), oral cyclophosphamide, methotrexate, TNF-α blockers, plasma exchange, mycophenolate mofetil, plus one related to newer developments in treatment with agents blocking the complement system and the possible role of sequential or combined therapies, mainly directed against B cells.

Introduction

Granulomatosis with polyangiitis (GPA, Wegener's) and microscopic polyangiitis (MPA) are small-vessel systemic vasculitis associated with antineutrophil cytoplasmic autoantibodies (ANCA) (1). Prior to the introduction of current standard treatment, GPA had a mortality rate of 80% within the first year (2). Forty years after first use of cyclophosphamide (CYC) as effective therapy in ANCA-associated vasculitis (AASV), survival is close to 80% at 5 years, but morbidity and drug-related toxic effects are still frequent (3-5). Although treatment options have increased in the last decade, with other immunosuppressives, biological drugs and plasma exchange (PLEX) (6), several questions remain unanswered. We have developed on some based on available evidence.

A MEDLINE search for English-language articles published between January 1970 and November 2012 was done. Terms included *ANCA-associated vasculitis, granulomatosis with polyangiitis, Wegener granulomatosis, microscopic polyangiitis, renal limited vasculitis* and *necrotising glomerulonephritis* plus combinations with *treatment, therapy, refractory, cyclophosphamide, methotrexate, TNF-α blockers, etanercept, infliximab, adalimumab, certolizumab, golimumab, plasma exchange, plasmapheresis, mycophenolate mofetil, rituximab, intravenous immunoglobulin, and complement system*. We identified and sought relevant articles from the references listed in retrieved articles. Late-breaking communications from international meetings were reviewed. Both authors reviewed wholly relevant articles.

Conundrum 1: Which is the best glucocorticoid regime and how long should it be used?

Although glucocorticoids (GC) are the cornerstone of the treatment, the optimal initial dose, tapering scheme and duration for remission-induction and maintenance phases are not well established.

Initial dose

It is common to start the with prednisone (PDN) or prednisonole at 1 mg/kg/day (maximum 60-80 mg/d) (6). In addition, in severe disease, pulsed

methylprednisolone is used (7 to 15 mg/kg, max 500-1000 mg qd for 3 consecutive days) (6, 7). Although common practice (7-12), these schemes are empirical, unsupported on evidence-based studies. Thus, best initial PDN (or equivalents) doses are debatable.

GC exert their anti-inflammatory and immunosupressive actions through genomic and non-genomic pathways (13, 14). Recent investigations reveal that the genomic pathway (responsible of inhibition of many pro-inflammatory molecules, but also toxic effects) is fully activating at PDN doses between 30 and 100 mg qd (15-18). This suggests that, at least theoretically, lower initial doses of PDN (0.5 mg/kg/d) could be as effective as higher to manage inflammatory disorders. There is evidence that schemes with reduced PDN or lower methylprednisolone doses, are non-inferior to standard high GC regimes in the treatment of lupus nephritis (19-21). This possibility, applied to the AASV merits formal evaluation. The PEXIVAS study (22) (*ClinicalTrials.gov Identifier: NCT00987389*) has introduced one low-dose GC arm (0.5 mg/kg) to evaluate if the reduced cumulative dosing regimen is as effective as standard doses for patients with severe AASV.

Tapering protocol

PDN tapering schedules are heterogeneous (7-12). Most protocols reach a dose of 20 mg qd at month two (12, 23), and no lower than 15 mg qd for the first 3 months of therapy (6). Decreasing GC protocols must be appropriate to reach disease control but to prevent the development of adrenal insufficiency. In this regard, it has been estimated that patients who receive ≥20 mg of PDN/day for more than 3 weeks will suffer hypothalamic-pituitary-adrenal (HPA)-axis inhibition (24); thus, PDN should be gradually tapered. However, some patients are unable to tolerate PDN doses below 10-15 mg/day without relapsing or experiencing smoldering activity (25-27), while others on GC physiologic doses (7.5-10 mg/d) cannot tolerate complete withdrawal. This is particularly true for GPA patients with granulomatous disease (28, 29). Accordingly, individual clinical criteria are necessary to achieve a balance between the minimum dose required to control activity and that predisposing to adverse effects.

Treatment duration

Total duration of GC therapy is controversial. It ranges from 6 to 18 months or more to control persistent systemic symptoms (7, 26, 30). The former is particularly possible when vasculitic manifestations, like glomerulonephritis or pulmonary haemorrhage due to lung capillaritis are present, but could take longer in those with predominant granulomatous manifestations. A recent guideline endorsed by EULAR recommends a maintenance dose of 10 mg qd or less during remission, but does not specify for how long (6).

Two recent studies (31, 32) evaluating the effects of duration of GC therapy in AASV are contradictory. In the first (31), -a metaanalysis of 983 patients-, a three-fold higher relapse rate took place in patients with GC discontinued within the first 12 months, compared with patients in which it was done after, or not at all (43% *vs*. 14%, respectively). These results contrast with those reported by McGregor *et al*. (32), who observed that length of GC therapy (shorter or longer than 6 months) had no effect on relapse number, progression to end-stage renal disease (ESRD) or death. Importantly, those treated beyond 6 months had significantly greater incidence of infections and new-onset diabetes mellitus.

In the absence of clear evidence to limit the PDN to ≤6 months, our opinion is to use it at low dose for long term in patients at high risk of relapse (upper respiratory tract disease, lung involvement, positive PR3-ANCA (33, 34)), in order to maintain control and reduce the accumulation of disease-related scarring. Also, it seems that some patients with persistant disease, especially with eye and retro-orbital involvement, and/or rhinosinusal disease, are not able to wholly withdraw low-dose GC.

Conundrum 2:
Who is a likely candidate for remission induction with methotrexate?

Treatment with long-term, high-dose CYC is associated with well-known toxicity at multiple levels that influence long-term morbidity and mortality of patients (5, 35). In an effort to reduce adverse effects (AE), methotrexate (MTX) has been used instead of CYC for remission induction (8, 12, 23, 27, 36-39). However, there are several questions about its use.

Dose

Added to GC, oral or parenteral formulations have been used starting at 15 mg/week (0.25–0.3 mg/kg) with increases of 2.5 mg weekly up to 20-25 mg/week between the first and third months (8, 23, 27, 36-39). Once remission is achieved, treatment should be continued for at least one year, probably 18-24 months, then tapered by 2.5 mg/week until stopped (8, 23, 30, 37).

Target population

MTX is recommended as an alternative in patients with AASV with early systemic disease (6). However, there is lack of an uniform definition for such (8, 12, 23, 27, 36-39), being currently described as non-organ or life threatening disease with a serum creatinine (Cr) level <1.35 mg/dL (40).

From published literature (8, 12, 23, 27, 36-39), MTX should be used in patients with recent GPA with or without constitutional symptoms and limited pulmonary involvement (focal pulmonary infiltrates or nodules with room air PO2 >70 mm Hg or pulse oximetry >92%), mild eye inflammatory disease (conjunctivitis, episcleritis, dacriocystitis), ENT manifestations, skin disease without extensive areas of gangrene, or musculoskeletal symptoms. MTX is not advised in cases of severe or life-threatening disease including acute renal failure, pulmonary haemorrhage associated with bilateral infiltrates, gastrointestinal or central nervous system involvement, progressive neuropathy, severe eye manifestations or heart failure due to pericarditis or myocarditis. In addition, chronic liver disease, alcoholism, pregnancy, pre-existing blood dyscrasias and age >75 years are current restrictions for MTX administration. It should be stressed that combination of co-trimoxazole – used previously for maintenance of remission in

GPA patients with limited disease (41) – and MTX is contraindicated as this may result in pancytopenia. Of interest, MTX has been related to inflammatory and/or fibrotic lung disease in 1-5% of rheumatoid arthritis patients (42). Although pre-existing lung disease is not considered a contraindication to MTX administration, it has been identified as risk factor for pulmonary toxicity (43). This is particularly true in MPA patients with associated interstitial lung disease (44, 45).

General efficacy and management of renal disease

Remission has been achieved in 60%-92% of patients treated with MTX and GC (8, 12, 36, 37, 46). In the only randomised clinical trial comparing CYC and MTX for remission induction, (NORAM study), MTX was non-inferior to CYC (8). In 100 patients (90% GPA), remission was achieved in 90% of those treated with MTX and in 93.5% treated with CYC. MTX was less effective in patients with extense disease and those with pulmonary involvement, requiring longer time to achieve remission. In addition, more MTX-treated patients relapsed (69.5% *vs*. 46.5%, similar to other reports, 36%–52% (25, 36, 37, 47)) and required higher cumulative doses of PDN (8.8 gr for MTX *vs*. 6.2 gr for CYC). No difference in infections was documented. Two drawbacks were the slow escalating schedule to reach target dose, which besides was 20–25 mg/week. If tolerated, it could have probably been of 30 mg/week.

NORAM's long-term follow-up was recently published. MTX-treated patients had shorter sustained remission than those who received CYC (48), cumulative relapse-free survival tended to be higher in CYC, and exposure to GC and other immunossupressive drugs was longer in MTX patients. However, no differences in cumulative survival (MTX 88% *vs*. CYC 90%), development of end-stage renal disease (ESRD), cancer or serious infections occurred.

There is debate about efficacy and safety of MTX in patients with renal involvement. MTX is mainly kidney-eliminated, and toxic potential is enhanced when renal clearance is impaired (49). In all referenced studies (8, 12, 23, 27, 36-39), patients with severe renal disease (Cr increase of >25% above baseline or Cr >2.5 mg/dL, red blood cell casts and proteinuria >1 gr qd) were excluded. However, good results have been reported in patients with mild renal disease (23, 48). In Langford *et al*. series (23), all patients (n=21) with active glomerulonephritis (mean Cr level of 1.4 mg/dL) achieved remission and 90% patients remained with stable or improved Cr levels at the end of follow-up (median of 6 years). It must be stressed that 60–70% of relapses in patients with maintenance therapy with MTX involve the kidneys (25, 47). However, progression to ESRD is rarely observed (2-5%) (12, 25, 47, 48), and patients with active renal manifestations without severe disease could be MTX-treated. We agree with this notion, but would achieve a maximal MTX dose (25–30 mg/week) faster than the NORAM trial did. They did it in 12 weeks, while we advocate doing it by 6–8 weeks. Also, some issues like dividing the dose on the same day or on 2 days, or giving it subcutaneously, which may, as in rheumatoid arthritis patients, increase absoption and bioavailability, could result favourable. However, in these diseases this has not been specifically proven. Regarding other manifestations, MTX seems adequate for predominant granulomatous disease.

Conundrum 3:
Is TNF-α inhibition out of sight?

Tumour necrosis factor-α (TNF-α) has been implicated in the pathogenesis of the AASV (50-54). *In vitro*, it enhances the ability of neutrophils to degranulate in presence of ANCA (54). In addition, high expression of TNF-α is detected at sites of vasculitis injury (52) and in the granulomas of patients with GPA (53). In the latter, increased circulating levels of TNF-α and its soluble receptor are present in active disase (50, 51).

Initial promising results with TNF-α inhibition (55, 56) led to the WGET trial, a randomised, placebo-controlled study. Results showed etanercept's inefficacy for remission maintenance, and a high rate of increased solid organ tumours (12, 57).

Although no randomised trial has established the efficacy of infliximab in AASV, information derived from small case series (58-60) or open label cohorts (61, 62) allows to speculate on its benefits. In five studies comprising 72 patients (GCA=53, MPA=19) (58-62), it induced remission in refractory or relapsing patients, mostly those who had received one or more immunosuppressives including CYC, MTX, azathioprine (AZA) or mycophenolate mofetil (MMF). Between 6 to 26 weeks, it induced remission or response in 85-90% of patients. In contrast, in a recently randomised study comparing the long term efficacy of RTX (n=8) and infliximab (n=9), only 33% of refractory GPA patients reached remission at 12 months (63). Also, it seems effective for controlling severe clinical manifestations like rapidly progressive glomerulonephritis, neuropathy, central nervous system manifestations (pachymeningitis and pituitary involvement), gastrointestinal vasculitis, severe ocular disease and refractory ENT and lung symptoms, and exhibits a GC-sparing effect. However, relapses are frequent with the use of infliximab (20–60%) even while still on therapy or after discontinuation. Some relapses have been successfully retreated with reintroduction of the biological. Regarding AE, infections are high (20%) with one fatality in 72 reported cases, while in relation to malignancy, one previously CYC-treated patient developed lymphoma.

Clinical differences in efficacy and side effects of etanercept and other anti TNF-α agents exist, in particular in granulomatous disorders such as Crohn's disease (64, 65). Variations in bioavailability and stability of union to the TNF-α molecule reside in the structure of different TNF-inhibitors. Etanercept is a fusion protein composed of two extracellular p75 TNF receptor domains (66), while infliximab is a chimeric monoclonal antibody (67). In contrast to etanercept, infliximab binds to circulating and membrane-bound TNF-α and induces apoptosis in cells expressing this molecule (64, 65, 68). In addition, infliximab has higher affinity and avidity, resulting in longer bind-

ing to TNF-α (61). Lack of favourable response observed in the WGET trial with etanercept was probably due to these differences but also because the dose used may not have been sufficient to achieve a therapeutic effect. Available information supports infliximab use as second line therapy for refractory or uncontrolled relapsing AASV patients. Concurrent use of CYC and anti-TNF-α is not advised, and patients that have received both medications should be followed closely.

There is one series of 14 patients with severe AASV (GPA=9, MPA=5) treated with adalimumab (69), in where remission was achieved in 78.5% of patients within the first 14 weeks of treatment, allowing concomitant GC reduction. Infections were reported in 3 patients (21%). Further studies are needed to gain insight about the potential place of adalimumab or infliximab for AASV.

Conundrum 4:
Plasma exchange in alveolar haemorrhage: as effective as in renal disease?

In patients with AASV and severe kidney disease, PLEX has reduced ESRD development, although it did not improve overall survival (70-76).

Diffuse alveolar haemorrhage (DAH) is present in 10-45% of patients with GPA and 10–30% with MPA (5, 38, 77-79). In the acute setting, 30% of DAH patients died, and in those who survived the initial episode, life expectancy at 1 and 5 years was reduced to 82% and 68%, respectively (79). Evidence for PLEX addition in AASV-DAH is scarce, heterogeneous and composed of case reports (80-85) and small retrospective series (86-89).

Most published case reports (80-83) include MPA, MPO-ANCA positive patients with respiratory failure. In them, combination of intense immunosuppression with CYC, IV-methylprednisolone and PLEX was associated with clinical and radiological improvement. However, populations were heterogeneous and the PLEX protocols used were diverse or not detailed. In the largest series (n=20 patients) (89), DAH resolved in 100% cases when treated with IV-methylprednisolone for 3 days and/or IV-CYC in combination with daily full-volume PLEX (average of 6.4 exchanges (range 4–9)). These results contrast with other two case series (87, 88), where mortality was as high as 36–42%, particularly in the first month. Based on the available information, it is not possible to unequivocally recommed PLEX as useful in DAH. In our limited experience (unpublished), we have had good results, similar to those of the MEPEX trial, in where some patients also had DAH, with resolution or improvement of this complication. The results of the PEXIVAS trial (22) will probably clarify if PLEX is useful for DAH. Five-hundred patients with DAH and/or severe renal disease will be randomised to adjunctive PLEX or no PLEX besides standard or reduced GC treatment.

Conundrum 5:
What is the current role of oral cyclophosphamide?

The current use of oral CYC is under review (4, 90) due to proved efficacy of pulsed IV-CYC (91, 92) and rituximab (RTX) (93-95).

In contrast to data regarding IV-CYC or RTX, there is long-term experience regarding oral CYC in AASV patients (4, 90), with remission or response in 77%-94% of cases, sustained remission in 43%-58% of cases (5, 7, 8, 33, 96), and 5-year survival between 70% to 90% (3, 97). Nonetheless, relapses are frequent in CYC-treated patients (29%-50%) and permanent disease morbidity is observed in 86% (5, 7, 8, 33, 96). The major disadvantage of oral CYC is high frequency of toxic effects, seen in 80% of individuals (8). Adverse effects (AE) associated with CYC are: amenorrhea (57%), cystitis (43%), leukopenia (35%), hair loss (17%), bladder cancer (2.8%), myelodysplasia (2%) and haematological malignancies (1 %) (5). Remarkably, 8% to 46% of GPA or MPA patients experience serious infections, with 20% mortality (5). Efforts to reduce the AE of high cumulative doses of CYC include dosage adjustment or IV administration, but although the latter and RTX are equally effective for inducing remission in patients with generalised AASV (91-94, 98, 99) they are not superior to oral CYC, remaining an option. Indeed, some patients who did not improve with IV-CYC, did with daily administration (100)

When compared to oral CYC, IV-CYC and RTX have a similar incidence of severe AE, except for leukopenia (91-94, 98, 99). Of note, infections rate has not decreased with RTX and IV-CYC (94, 101, 102). This probably reflects the effect of prolonged administration of high oral CYC doses used in older cohorts (3-5 mg/kg/d for severe disease) (5) in comparison to adjusted doses used in the most recent studies (1.5–2 mg/kg/d) (103).

Patients which seem to benefit most from oral CYC include those with generalised disease without predictors of relapse, *i.e.* PR3-ANCA+, upper respiratory tract, lung disease (33, 34, 96, 104), cardiac involvement or granulomatous predominant disorder (105), patients with active disease despite RTX, or those intolerant to it, and those with DAH severe enough to require mechanical ventilation or with rapidly progressive glomerulonephritis and serum Cr levels >4mg/dL. Additionally, oral CYC could also be an option for individuals in countries where the economic burden of biologics is very high. Patients preference may contribute to the regime choice once advantages and disadvantages are explained.

For those patients receiving oral CYC, we recommend an initial dose of 1.5–2 mg/kg qd (maximum 150 mg/day) for a minimum of 3, and a maximum of 6 months in non-refractory cases (92, 106, 107). Excellent previous reviews (92, 106, 107) have described dose adjustments, monitoring guidelines, and preventive measures regarding opportunistic infections, urinary and gonadal toxicity.

Conundrum 6:
Is MMF effective for either induction or maintenance therapy?

MMF selectively inhibits T and B cell proliferation by suppressing guanine synthesis and blocking DNA structure (108). It is extensively used in organ rejection prevention following renal, car-

diac or hepatic transplants (109, 110). In addition, MMF has been explored with good results in other autoimmune disorders, paticularly in lupus nephritis (111-113).

In AASV, MMF has been used for both remission induction (114-119) and maintenance therapy (117, 120, 121). Experience as induction therapy includes almost 100 patients reported in small case series (114, 116-119) and one single centre non-blinded clinical trial (115). In these studies, patients with GPA and MPA were treated with MMF instead of CYC because of intolerance or refractory/relapsing disease. Remarkably, half of these patients had mild to moderate active renal disease. Overall, complete remission was attained in 60%–82% of these refractory/relapsing cases (114-117) with daily doses of 1.5–3 g. Progression to ESRD was uncommon and, in approximately 60% of patients with kidney involvement, renal function remained stable or improved (114, 116-119).

Direct comparison between MMF and CYC for remission induction has been performed in a small single-centre trial (n=35, most patients MPO-ANCA+) (115). Remission rate at 6 months was higher with MMF than CYC (77.8% *vs*. 47.1%), with renal function improvement. In contrast, results of an international, multi-centre, controlled trial (MYCYC) (122), -which was ultimately underporwered-, patients were randomised to MMF (2-3 g/day) or 6–10 pulses of IV CYC (15mg/kg). In the preliminary results, recently published in abstract form, remission at 6 months with MMF was 66% *vs*. 69% with CYC, but confidence intervals were wide and surprisingly, overall expected remission rates were inferior to estimated; also, MMF did not demostrate significant glucocorticoid-sparing effect, and both drugs were associated with similar rates of adverse effects.

Regarding maintenance therapy, case series (117, 120, 123, 124) summing approximately 70 patients reported stabilisation of renal function and decreased activity indices in the majority of patients. However, relapses are common, presented in 10%–76% of cases (117, 120, 123, 124). More importantly, the results of an open-label, randomised multi-center trial (IMPROVE) (121), showed that MMF was less effective than AZA for the prevention of relapses in AASV. In 156 patients with newly diagnosed GPA/MPA, MMF (2 g/day) was compared to AZA (2 mg/kg/day) for maintenance after induction of remission with CYC. At median follow-up of 39 months, relapses were significantly more frequent among those in the MMF limb compared with the AZA arm (55% *vs*. 38 %). Also, in the referenced studies (114, 115, 117, 121), MMF related AE were commonly observed (22%–71%), mostly infections and/or gastrointestinal intolerance.

Based on the available information, it remains to elucidate if MMF could be considered as a first line therapy for remission induction, and in maintenance AZA and MTX seem better. However, it can be considered as reasonable option for patients with non-life threatening relapsing or refractory disease.

Conundrum 7:
Which recent advances seem promising?

Through this review we have discussed on unsolved dilemmas in treatment of AASV. There is clearly a need for newer therapies with better efficacy and fewer adverse effects. In the last 2 years, with better understanding of AASV pathogenesis and efforts of collaborative groups around the world, new strategies to achieve and maintain remission have emerged as potential options (125). Belimumab, abatacept or gusperimus could be new future alternatives, provided extended information and precise situations in which their role is endorsed develop. However, in the final part of this paper we will review two exciting options with known drugs: 1) combination of RTX with high-dose intravenous immunoglobulin (IVIG) and 2) inhibition of the complement system.

1) *The hypothetic role of combined or sequential schemes of B-cell depletion therapy and IVIG*

Two randomised clinical trials, *i.e*. RAVE (94) and RITUXVAS (93) and several case series and cohort studies (126-141) (pooled n=~250 patients), demonstrated that RTX combined with GC is not inferior as standard therapy with CYC for remission induction of patients with newly severe AASV and, probably more effective in refractory/relapsing cases. On the other hand, small case series (142-146) have showed that administration of high-dose IVIG (total dose 2 g/kg) in cases with uncontrolled and persistent ANCA disease resulted in improvement of disease activity in 50%-80% of patients. However, in these last studies low rate of complete remission was attained (145) and benefits of IVIG were limited to the first 3 months after infusion (144, 146).

Combination schemes using RTX and IVIG have already been tried with good results in a case of an acquired inhibitor of coagulation factor VIII (147), for renal transplant recipients (148, 149) and in patients with pemphigus vulgaris. (150, 151). Importantly, a favourable safety profile was reported in all (152). RTX and IVIG share some mechanisms of action which can act synergistically, such as B-cell apoptosis induction, antibody-dependent cellular cytotoxicity, modulation of several pro-inflammatory cytokines and improvement of the suppressive functions of Treg (152-154). In addition, some of their immune-modulatory effects can be complementary. For example, IVIG may act rapidly reducing the immune activity by interacting with Fc-receptors of inflammatory cells (155, 156) and by the presence of anti-idiotypic antibodies that could theoretically neutralise ANCA (157-159). These high-speed, short-lived effect of IVIG can be followed by the more prolonged and durable actions of RTX (153). As experience with combination schemes is virtually inexistent in AASV, it remains to determine the optimal dose for each drug, suitability of concomitant or sequential administration and, importantly, the safety profile. However, we think such an option deserves formal evaluation.

2) *Inhibition of the complement system in light of newer discoveries*

Recent data suggest a role for the the

complement system (CS) in the pathogenesis of AASV (reviewed in (160-162)). Briefly, based on mice models of anti-MPO-induced glomerulonephritis (163, 164), it has been demostrated that the development of renal disease and vascular inflammation depend on complement activation (165, 166), specifically, the alternative pathway (166). Of note, C5a and its receptor C5aR appear to be fundamental for induction of damage in these models (164, 165). In addition, *in vitro* studies have shown that ANCA-stimulated neutrophils release factors (probably properdin) that cause complement activation with generation of C3a (166) and C5a (164), initiating the cascade that culminates in inflammation and damage of vessel walls. In humans there is evidence to suggest that the alternative pathway is involved in vasculitic renal damage. Complement factors C3c, C3d and membrane attack complex (MAC) have been detected in renal specimens of patients with ANCA-associated glomerulonephritis (167, 168). Interestingly, demostration of glomerular deposition of C3c was associated with higher levels of proteinuria and poorer renal function (167). Finally, a recent published study have disclosed elevated plasma and urinary concentrations of C5a in 24 patients with active MPO ANCA-vasculitis with glomerular disease (169).

Based on these data, blocking the activity of the complement system appears interesting, particularly C5 inhibition. For this purpose, eculizumab, a monoclonal antibody (mAb) that binds to C5, blocking its activation seems a logical choice. In fact, a clinical trial targeting complement activation in AASV with eculizumab is currently recruiting patients (*ClinicalTrials.gov Identifier: NCT01275287*). In this study, patients with active ANCA vasculitis and renal disease will be randomised to receive conventional therapy in addition to the biologic therapy or placebo. Other inhibitory molecules of the C5-C5aR axis that could be candidates for AASV treatment include pexelizumab (mAb targeted C5), neutrazumab (antibody blocking the C5aR), and molecules like ARC905 and CCX168 (170).

Conclusion

Current treatment of AASV is the result of multiple contributions and refinements made in the last 40 years. Major progress has been made in patient survival. However, we face now chronic diseases that can severely impair the quality of life. Therefore, finding new and better treatments is a priority for those dedicated to the study of systemic vasculitides.

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