CHAPTER 11

Advances in the Discovery of C5a Receptor Antagonists

Jay P. Powers, Daniel J. Dairaghi and **Juan C. Jaen**

Contents

1. INTRODUCTION

The complement system plays a central role in the generation of innate and adaptive immune responses to infectious agents, foreign antigens, virus-infected cells, and tumor cells. The complement system consists of more than 30 components which play an essential role in the responses to infection and injury. The complement cascade may be initiated *via* the classical (triggered by immune complex formation), lectin (antibody independent), or alternative pathways, all of which converge at C3 (Figure 1). Activation of the complement pathway generates biologically active fragments of complement proteins, for example, C3a, C4a, and C5a anaphylatoxins and C5b-9 membrane attack complexes (MAC), all of which

ChemoCentryx Inc., 850 Maude Avenue, Mountain View, CA 94043, USA

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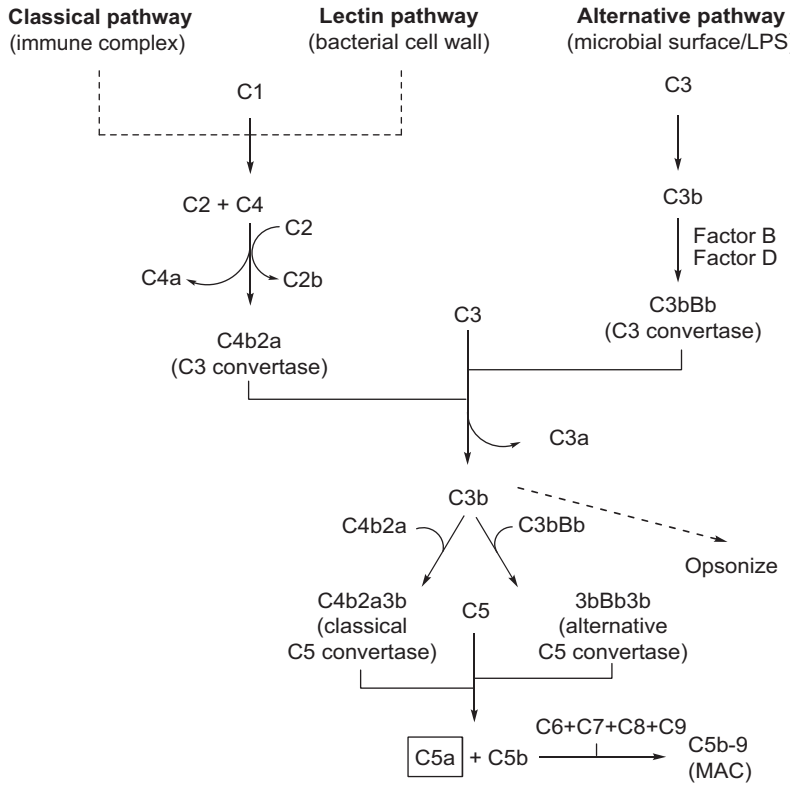


Figure 1 The complement cascade, leading to production of the anaphylatoxin C5a.

mediate inflammatory responses by inducing leukocyte chemotaxis, activating macrophages, neutrophils, platelets, mast cells, and endothelial cells and increasing vascular permeability, cytolysis, and tissue injury. Inappropriate or excessive activation of the complement system, in general, and formation of the C5a anaphylatoxin, in particular, can lead to harmful consequences due to severe inflammation and resulting tissue destruction. These consequences are clinically manifested in various human pathologies, ranging from the acute setting of septic shock and ischemia/reperfusion injury to chronic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), transplant rejection, macular degeneration, vasculitis, and psoriasis, among others. The complement system has long been an attractive target for drug discovery [1], and interest in targeting the C5a receptor [2–4] has been widespread since initial reports on small molecule antagonists in the early 1990s. However, targeting the C5a/C5a receptor pair has been extremely challenging, with only a single entity (eculizumab, an anti-C5 antibody) advancing to

approval over that same 20-year period. In this chapter, we review the recent advances in the discovery of peptide and small molecule antagonists of the C5a receptor, with a focus on results that have come to light since 2004, when the topic was last reviewed in Annual Reports [2].

1.1. The C5a receptor

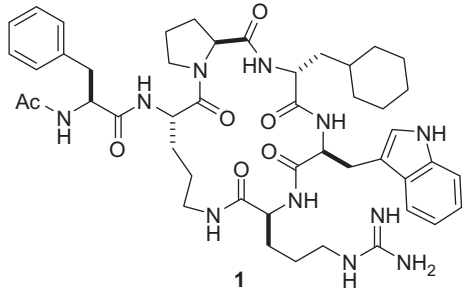
C5a is one of the most potent proinflammatory mediators of the complement system, being at least 100 times more potent than C3a. This 8.3 kDa polypeptide, along with a C5b fragment, is produced by enzymatic cleavage of a C5 precursor during activation of any of the three complement pathways. C5a induces expression of adhesion molecules and chemotactic migration of neutrophils, eosinophils, basophils, and monocytes. It also mediates inflammatory reactions by causing smooth muscle contraction, increasing vascular permeability, inducing basophil and mast cell degranulation, and releasing lysosomal proteases and oxidative free radicals. The anaphylactic and chemotactic effects of C5a are mediated through its interaction with the C5a receptor (C5aR, CD88), a 350-residue GPCR expressed on neutrophils, monocytes, basophils, eosinophils, renal glomerular tissues, lung smooth muscle, and endothelial cells.

Approaches to pharmacological intervention targeting C5aR have focused on two general areas. In the first, targeting of C5aR itself by small molecule, peptide, and anti-C5aR antibodies offers a direct and selective inhibition of C5aR function. In the second approach, binding of antibodies or aptamers to C5 prevents its cleavage to C5a and C5b, indirectly preventing activation of C5aR but also impacting formation of the MAC (Figure 1), which is critical in the clearing of many bacterial infections through MAC-mediated cell lysis. Although inhibition of MAC formation can be a successful strategy for some therapeutic indications (Sections 5 and 6), it is important to note that the two approaches can result in very different biological outcomes, as inhibition of MAC formation can also create some unique risk of infection [1].

2. PEPTIDE AND LARGE MOLECULE AGENTS

Truncated C5a C-terminus hexapeptide derivatives served as the starting point for the discovery of several peptidomimetic antagonists of C5aR. The conformationally constrained cyclic antagonist **1** (PMX-53, 3D53, AcF-[OP-dCha-WR]) was designed after ^{1}H NMR experiments suggested a turned cyclic conformation of prototypical linear hexapeptides [5,6]. A moderate scale (50–100 g) solution phase synthesis of **1** has been reported [7]. Numerous preclinical *in vitro* and *in vivo* studies have been described utilizing **1**, including rat pharmacokinetics [8] and efficacy in

animal models of monoarticular arthritis, LPS-induced neutropenia, ulcerative colitis, dermal and peritoneal inflammation, and assorted ischemia/reperfusion injuries [2–4,9].



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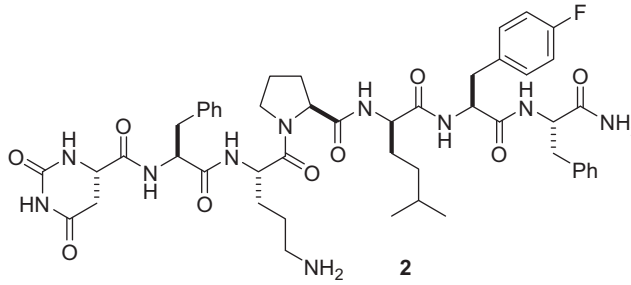
Peptide **1** was shown to be safe and well tolerated in several Phase 1 clinical trials, both in healthy volunteers and in patients with psoriasis and arthritis [10]. A small Phase 1b/2a clinical trial performed with **1** in patients with active RA [11] failed to show a decrease in cell infiltration, synovial inflammation, or changes in key biomarkers associated with clinical efficacy. However, it must be noted that low drug exposure observed in the study, combined with the potential effect of plasma protein binding, may have provided insufficient receptor coverage for efficacy. Compound **1** does not appear to be undergoing any additional clinical activity at the present time.

A peptidomimetic antagonist, JPE1375 (**2**), was derived from the systematic deconstruction of **1** [12]. More specifically, JPE1375 resulted from replacement of the arginine in **1** with the lipophilic phenylalanine, cleavage of the macrocyclic ring, and replacement of the terminal NAc moiety with hydroorotic acid. Compound **2** was reported to have similar functional potency to **1** as measured by inhibition of C5a-induced glucosaminidase release in C5aR-transfected RBL cells (IC_{50} = 39 and 29 nM for **2** and **1**, respectively) and in binding to HEK293 cells (IC_{50} = 111 and 104 nM for **2** and **1**, respectively). Potency on the mouse receptor was significantly greater for **2** than for **1** as measured by chemotaxis in mouse J774.1 cells (IC_{50} = 0.42 vs. 7.1 μM). Stability in human liver microsomes was significantly improved for **2** (80% remaining at 1 h) *versus* **1** (10% remaining after 1 h). The *in vivo* efficacy of **2** was tested in the reverse passive Arthus reaction, a mouse model of immune complex-mediated disease. JPE1375 (dosed at 1 mg/kg, i.v.) significantly reduced the influx of neutrophils into the peritoneum after simultaneous i.v. challenge with OVA peptide and i.p. challenge with an anti-OVA antibody. In a model of tubulointerstitial fibrosis, **2** (dosed at 0.63 mg/kg/day, i.p.) resulted in significant impact on markers of renal fibrosis, including fibronectin

protein expression, Sirius Red staining, and PDGF-B mRNA expression after 5 days [13].



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3. MACROMOLECULES

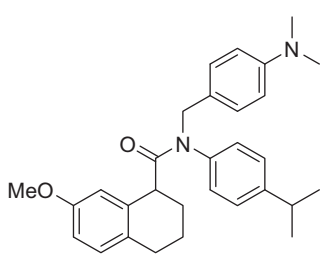
Non-antibody macromolecules have been actively pursued as antagonists of C5aR. The 121-residue immune evasive protein excreted by *Staphylococcus aures*, chemotaxis inhibitory protein of *S. aures* (CHIPS) binds to C5aR. Recombinant $CHIPS_{28–149}$ inhibits the binding of C5a to C5aR with an IC_{50} of 6.7 nM without inhibiting the binding of C5a to the closely related C5L2 receptor [14]. While $CHIPS_{28–149}$ does block binding of C5a-des-Arg to C5L2 with an IC_{50} of 274 nM, it lacks affinity for the closely related ChemR23, FPRL1, or FPRL2 receptors. Although CHIPS is a potent antagonist of C5aR, it is also highly immunogenic, and antibodies to CHIPS have been identified throughout the general population [14], making the therapeutic use of CHIPS itself untenable. Several groups have sought to modify CHIPS by removing or replacing the multiple immunogenic epitopes. In this regard, a 50-residue adapted peptide (CHOPS), designed to maintain binding while reducing the interaction with human IgG, has been reported with micromolar affinity for a model peptide comprising residues 7–28 of the C5aR N-terminus [15].

ADC-1004 is a truncated and mutated form of CHIPS designed by directed evolution [16] to lower the interaction with human IgG and is postulated to inhibit the binding of C5a by interacting with the N-terminal site on C5aR. ADC-1004 binds to, but does not activate, C5aR [17,18]. ADC-1004 has been tested in a porcine ischemia–reperfusion model, reducing myocardial infarction (infarct size) by 21% ($p = 0.007$) when dosed 175 mg *via* i.v. bolus [19]. No clinical activity has been disclosed for ADC-1004 [20].

4. SMALL MOLECULE AGENTS

Many small molecule C5aR antagonists have been disclosed over the past two decades [2–4]. Clinical efficacy with the first generation small molecules was very limited, but some of the second and third generation antagonists have shown considerable promise.

W-54011, **3**, was identified using a high-throughput screen followed by lead optimization [21]. W-54011 is a potent inhibitor of C5a binding to human neutrophils in cell culture buffer with a K_i of 2 nM and is also a functional inhibitor of Ca^{2+} mobilization ($IC_{50} = 3$ nM) and C5a-mediated chemotaxis ($IC_{50} = 3$ nM) in human neutrophils [21]. In the same report, the IC_{50} values for **1**, in Ca^{2+} mobilization and chemotaxis, were 55 and 18 nM, respectively. W-54011 demonstrated potent, and species selective, inhibition of C5a-mediated Ca^{2+} flux in neutrophils from humans, cynomolgus monkeys, and gerbils, but not from mice, rats, guinea pigs, rabbits, or dogs. W-54011 did not block Ca^{2+} mobilization stimulated by fMLP, PAF, or IL-8 and demonstrated good selectivity for C5aR. In a C5a-induced neutropenia gerbil model, W-54011 (dosed p.o.) inhibited C5a-induced neutropenia in a dose-dependent manner, with complete abrogation of the neutropenia at the top 30 mg/kg dose. W-54011 was also investigated for its ability to ameliorate established collagen-induced arthritis in cynomolgus monkeys [22]. Treatment with W-54011 for 15 days (30 mg/kg, p.o.) resulted in significant reduction in joint swelling within 2 days, with continued suppression for the length of the experiment. In the same study, W-54011 also significantly ameliorated radiographic scores of joint destruction. Two recent patent applications have published that disclose a closely related small molecule (**4**) and its associated salts, as well as the preparation of an optically pure intermediate used in its synthesis [23,24]. Although no data for compound **4** has been published in the scientific literature, these applications may indicate a special interest in this specific compound.



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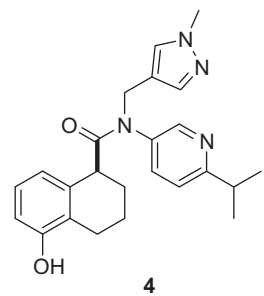

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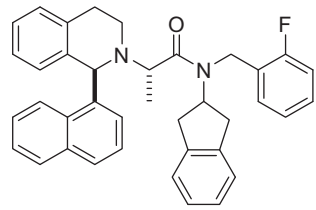
NDT9520492 (**5**) has been investigated for activity on the C5a receptor from multiple species [25]. Overall C5aR sequence homology between

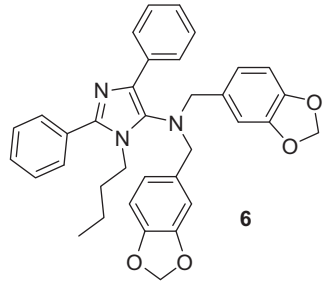
human and nonhuman primate C5aR is >95%, but it is generally only 65–75% between human and nonprimates. Based on alignment of C5aR sequences, it was shown that a tryptophan residue in the transmembrane domain V is the only transmembrane domain amino acid unique to species (*i.e.*, gerbil, human, and nonhuman primate) that recognize small molecule C5aR antagonists. In binding experiments, NDT9520492 inhibited [^{125}I]-C5a binding with IC_{50} values of 29 nM (human C5aR), 109 nM (gerbil C5aR), and >10,000 nM (mouse C5aR), while in the same experiment, W-54011 and AcF-[OP-dCha-WR] inhibited binding with the same pattern (W-54011: 4, 13, and >10,000 nM, respectively, AcF-[OP-dCha-WR]: 25, 456, and >10,000 nM, respectively). Interestingly, site-directed single-point (L214W) mutagenesis of the mouse receptor to install the tryptophan residue in transmembrane domain V resulted in dramatic increases in potency inhibition of mL214W-C5aR [^{35}S]GTPγS binding for NDT9520492 and W-54011, but not for cyclic peptide AcF-[OP-dCha-WR] [25].



5

NDT9513727 (**6**) has been described as a potent and competitive antagonist of C5aR with properties consistent with inverse agonism [26]. NDT9513727 has been well characterized and displayed an IC_{50} of 11.6 nM in a [^{125}I]-C5a binding assay. NDT9513727 inhibited C5a-stimulated responses, including Ca^{2+} mobilization, oxidative burst, degranulation, chemotaxis, and cell surface CD11b expression in assorted cell types with IC_{50} values from 1 to 9 nM. The compound was selective against C5L2 and in a Cerep screen, and was potent in human, cynomolgus monkey, and gerbil C5aR, but was inactive in the rat, mouse, and dog receptors. NDT9513727 was found to have reasonable PK in cynomolgus monkeys with moderate bioavailability ($F = 26\%$). NDT9513727 was examined in a C5a-induced neutropenia model in cynomolgus monkeys and exhibited 66% inhibition of C5a-stimulated neutropenia at 25 mg/kg dosed orally (plasma concentration = 410 ± 218 nM). In an *ex vivo* assay of C5a-mediated upregulation of CD11b on human blood granulocytes in fresh human whole blood, **6** displayed concentration-dependent inhibition with an IC_{50} of 0.6 μM. The concentration required to reach approximately 50% inhibition was similar in the cyno neutropenia and *ex vivo* human whole blood CD11b expression assays. Modest potency *in vivo* in

the cynomolgus neutropenia and in the whole blood CD11b upregulation assay *ex vivo* compared to the potency in the serum-free *in vitro* assays was attributed to the high protein binding (>99%) in human plasma. The use of the physiologically relevant (whole blood, primary cells, presence of plasma proteins) CD11b assay and its correlation with the *in vivo* assay results highlights the importance of the inclusion of these types of effects in assays that hope to predict C5aR receptor blockade *in vivo*.



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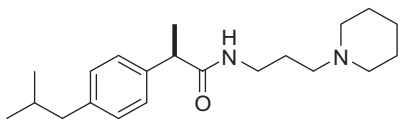
NGD 2000-1 (structure undisclosed) has been described as a substituted tetrahydroisoquinoline C5a antagonist [3]. NGD 2000-1 entered Phase 2 clinical trials in both asthma and RA patients. In patients with mild to moderate asthma, NGD 2000-1 did not demonstrate a therapeutic benefit (primary endpoint Forced Expiratory Volume in 1 second, FEV1) [4]. In patients with mild to moderate RA, NGD 2000-1 did not demonstrate an effect in the trial's primary endpoint (changes in C-reactive protein, CRP); however, it did demonstrate a statistically significant change in the Subject Global Assessment of Disease activity at a dose of 100 mg twice daily. Subsequent *post hoc* analysis of the ACR20 response revealed a statistically significant response at the highest dose tested [27]. However, during Phase 1 clinical trials, NGD 2000-1 was found to inhibit cytochrome P450 3A4 [3,28,29], limiting dose levels, which would not allow a sufficient therapeutic window at the doses that were believed to be required for future development in patients with RA [27], and development of NGD 2000-1 has been abandoned [3,28].

SAR studies based on a class of noncompetitive allosteric inhibitors of chemotactic receptors [30] led to **7**, a dual inhibitor of both C5a- and IL-8-mediated human granulocyte chemotaxis [3,31,32]. Descriptions of the potency of **7** against C5a-mediated activity are unclear in the original patent application [31] and in the review literature range from tens of nanomolar [32] to tens of micromolar [3]. Recently, related structures have been described in the patent literature which are selective for inhibition of C5a-mediated human granulocyte chemotaxis and which lack IL-8 activity [33,34], as represented by compound **8**, which showed 60% inhibition of C5a-induced chemotaxis when tested at 10 nM [34].



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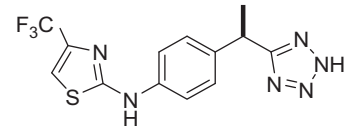

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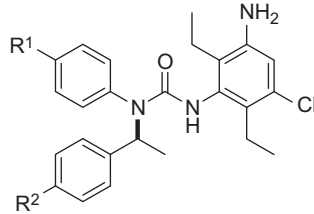
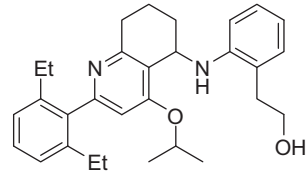
JSM-7717 is a small molecule C5aR antagonist in preclinical development [35] and belongs to a genus of structures represented by compounds **9**–**11** [36]. Compound **9** inhibited C5a-induced enzyme release with an IC_{50} of 3 nM, while **11** inhibited [^{125}I]-C5a binding to C5aR in hC5aR-HEK293 cells with an IC_{50} of 43 nM, and inhibited *E. coli*-induced oxidative burst in fresh human whole blood with an IC_{50} of 620 nM. Both **9** (1 mg/kg, i.v.) and **10** (3 mg/kg, i.v.) were examined in a C5a-induced neutropenia model in male gerbils and both demonstrated inhibition in this acute model. Although the patent application does not explicitly disclose the structure of JSM-7717, it may be deduced to be either **9** or **10** based on the identifiers in the neutropenia results (Figure 2 in Ref. 36) as compared with the written description.



9: R^1 = NHMe, R^2 = Cl
10: R^1 = Et, R^2 = Cl
11: R^1 = NHMe, R^2 = H

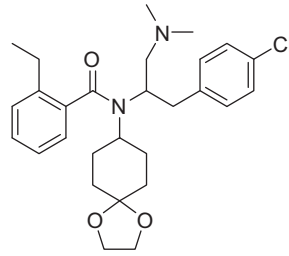
A series of 5,6,7,8-tetrahydroquinoline C5a antagonists are exemplified by **12** [37–39]. Compound **12** inhibited C5aR in a Ca^{2+} mobilization assay with an IC_{50} of 7.3 nM, and had a K_i in a [^{125}I]-C5a competition binding assay in the single-digit nanomolar range [37]. Similar compounds showed moderate to medium clearance when dosed i.v. in rat, and moderate to good bioavailability [38,39].



12

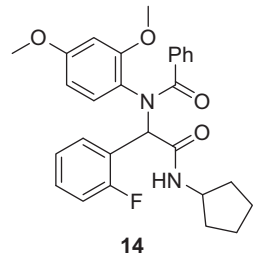
A high-throughput screening effort led to the discovery of CP-447,697 [40], which was further elaborated to **13** [41]. **13** inhibited [^{125}I]-C5a binding in U937 cells with an IC_{50} of 27 nM and inhibited C5a-mediated

elastase release in human neutrophils with an IC_{50} of 25 nM. In a CD11b upregulation assay in fresh human whole blood, **13** exhibited a potency of 4,800 nM (the concentration required to shift the dose–response curve for the C5a-induced upregulation of CD11b in human whole blood by 10-fold). The investigators postulated that the very high shift in potency in the presence of human whole blood was directly related to the very high human plasma protein binding (99.6%). The high protein binding was attributed to the high lipophilicity of **13**, which led to the abandonment of further lead optimization efforts [41].



13

High-throughput screening led to the discovery of **14** [42]. Compound **14** inhibited C5a-induced Ca^{2+} mobilization in hC5aR transfected 293 cells with a pIC_{50} of 7.6 and inhibited C5a-stimulated Ca^{2+} mobilization in human neutrophils with a pA_2 of 7.4. The compound was inactive in dog, rat, and mouse receptors. Due to an apparently insurmountable disconnect between potency and metabolic stability, the series was not progressed further into additional lead optimization [42].



14

CCX168 (structure not disclosed) is a small molecule that potently inhibits [^{125}I]-C5a binding to C5aR with an IC_{50} of 0.62 nM, C5a-mediated chemotaxis with an IC_{50} of 0.25 nM (both in human U937 cells), and C5a-mediated Ca^{2+} mobilization with an IC_{50} of 0.4 nM in human monocytes in cell culture buffer [43]. CCX168 is highly selective with no activity on the closely related C5L2, C3aR, ChemR23, GPR1, and FPR1 receptors. CCX168 remained highly potent under physiologically relevant conditions and inhibited C5aR-mediated chemotaxis in fresh human whole

blood with an A_2 of 1.7 nM, and inhibited C5aR-mediated CD11b upregulation on human neutrophils in fresh whole blood with an A_2 of 4 nM. The compound was potent on cynomolgus monkey receptor but inactive on mouse and rat receptors. CCX168 was tested *in vivo* in human C5aR knock-in mice (similar *in vitro* potency) and demonstrated inhibition of C5a-induced leukopenia with an ED_{50} of ~0.03 mg/kg. Oral dosing of CCX168 in a mouse model of vasculitis in humanized mice markedly suppressed the induction of glomerulonephritis by antimyeloperoxidase (anti-MPO) IgG. Daily dosing of CCX168 (30 mg/kg) reduced glomerular crescent formation from 29.3% (vehicle alone) to 3.3% with CCX168 ($p < 0.0001$), and glomerular necrosis was reduced from 8.2% to 1.1% ($p < 0.0001$) [44]. Urine protein, leukocytes and RBCs, and serum BUN and creatinine were reduced as well. A low dose of 0.1 mg/kg/day caused a 30% reduction in crescents. The lowest dose that produced near-maximal therapeutic benefit was 4 mg/kg bid, where plasma levels ranged from 35 to 200 ng/mL throughout the day and C5aR blockade ranged from 95% to 99% based on the potency in whole blood CD11b upregulation [44]. CCX168 is currently in human clinical trials (*vide infra*).

5. CLINICAL UPDATE

ARC1905 is an anti-C5 RNA aptamer that inhibits the cleavage of C5 into C5a and C5b [1], for which detailed characterization data has not been published. ARC1905 is currently in two Phase 1 clinical trials in patients with age-related macular degeneration (AMD). The first trial is to examine safety and tolerability of ARC1905 intravitreous injection in subjects with geographic atrophy secondary to dry AMD [45]. The second trial is intended to evaluate the safety, tolerability, and pharmacokinetics of multiple doses of ARC1905 intravitreous injection when administered in conjunction with multiple doses of Lucentis® 0.5 mg/eye, or with a single induction dose of Lucentis® 0.5 mg/eye in patients with subfoveal neovascularization (CNV) secondary to AMD [46].

CCX168 (structure not disclosed) is a sub-nanomolar C5aR antagonist across many assay formats in cell culture buffer (*vide supra*) that inhibits C5aR-mediated chemotaxis in human whole blood with an A_2 of 1.7 nM and inhibits C5aR-mediated CD11b upregulation on human neutrophils in whole blood with an A_2 of 4 nM [43]. CCX168 has been evaluated in Phase 1 single and multiple dose clinical trials. In an *ex vivo* pharmacodynamic analysis of C5aR receptor coverage performed as part of the Phase 1 trial, CCX168 was found to reduce C5a-induced CD11b upregulation on blood neutrophils 12 h following a single dose of 100 mg. Plasma levels of

CCX168 of 197 ng/mL (~400 nM) were reached after the 100 mg dose, which far exceeds the levels required in an anti-MPO mouse model for near-maximal prevention of glomerulonephritis [44]. At this dose, terminal plasma half-life was ~29 h. On day 7 of the 30 mg CCX168 bid regimen, greater than 90% receptor coverage was maintained throughout the day. The combined pharmacokinetic and pharmacodynamic data for the Phase 1 trials and preclinical studies indicated that 30 mg CCX168 dosed bid in humans should result in greater than 90% C5aR coverage in blood at all times, believed to be optimal for testing C5aR antagonism in Phase 2 trials. Interest has been expressed in further studies to examine CCX168 as a potential therapeutic for antineutrophil cytoplasmic antibody (ANCA) related vasculitis [43,44].

NN8209 is an anti-C5aR antibody currently in a Phase 2 clinical trial in patients with RA to assess the safety, tolerability, and pharmacokinetics of NN8209 in combination with stable doses of methotrexate [47]. In this trial, NN8209 is dosed once weekly subcutaneously over a 3-week period.

MP-435 is a small molecule C5aR antagonist which is currently in a randomized, double blind, placebo controlled Phase 2 efficacy trial in combination with methotrexate in patients with RA [48]. Although the structure of MP-435 has not been disclosed, it is possibly related to **4** (*vide supra*).

Eculizumab (Soliris®) is a recombinant humanized monoclonal $IgG_{2/4}\kappa$ 148 kDa anti-C5 antibody produced by murine myeloma cell culture and approved for use in the United States and European Union in 2007 for the treatment of paroxysmal nocturnal hemoglobinuria (PNH, Section 4). Human pharmacokinetics have been described [49]. Eculizumab has undergone trials in many indications, including psoriasis, RA, SLE, and cardiovascular indications [1,3]. Numerous clinical trials are ongoing or recruiting with eculizumab, including Phase 2 studies in ANCA-associated vasculitis [50], AMD [51], dense deposit disease and C3 nephropathy [52], kidney transplant [53,54], myasthenia gravis [55], and atypical hemolytic uremic syndrome (aHUS). Recent Phase 2 trial results in an interim analysis of 17 patients with aHUS who were resistant to plasma therapy and were treated with eculizumab resulted in a significant ($p < 0.0001$) increase in platelet count observed with treatment compared to baseline [56]. Another recent study summarized results from an interim analysis of 15 patients with aHUS on chronic plasma therapy treated with eculizumab for at least 12 weeks showed a significant 87% (13/15; 95% CI 60–98) number of patients achieved TMA event free status (Thrombotic MicroAngiopathy; defined as stable platelet counts, absence of plasma therapy, and no new dialysis) [57]. A shorter acting variant of eculizumab, pexelizumab, no longer appears to be under active development.

6. MARKETED AGENTS

Eculizumab (Soliris®) is a recombinant humanized monoclonal anti-C5 antibody, approved in 2007 for the treatment of PNH. The pathophysiology of PNH and treatment of the condition with eculizumab in clinical trials have been reviewed [58]. Clinical features of PNH are caused by the MAC attack on erythrocytes, and prevention of MAC formation is believed to protect PNH red blood cells in circulation, and in this context, treatment with eculizumab prevents C5b formation which is necessary to form the MAC. In the treatment of PNH, eculizumab is dosed 600 mg *via* i. v. infusion every 7 days for the first 4 weeks, followed by 900 mg 7 days later, and then 900 mg every 14 days thereafter, for a total of ~25 g of antibody/patient/year. Eculizumab reduces production of C5b (and thus MAC formation), which is expected to lead to higher susceptibility to bacterial infection. As it is also known that people with genetic deficiency for terminal complement proteins (*i.e.*, the MAC) have an increased risk for infection, particularly by *Neisseria meningitides*, patients on eculizumab are vaccinated with a meningococcal vaccine as a prophylactic measure before starting treatment. Sales of eculizumab were US $541M in 2010 [59].

7. CONCLUSION

Over the past decade, significant advances have been made toward the goal of targeting the C5a/C5aR axis, with one agent (eculizumab) approved and five agents currently reported to be undergoing clinical trials. Activity remains split between targeting C5 (anti-C5 antibodies and aptamers) and C5aR itself (small molecule C5aR antagonists and anti-C5aR antibodies). Discovery of small molecule C5aR antagonists with properties appropriate for advancement into the clinic has continued to advance, and the first anti-C5aR antibody has begun clinical trials as well. With two C5aR antagonists in Phase 2 clinical trials for RA, it will be very interesting to see results which follow up on the early, if limited, success of the last C5aR antagonist explored in this indication (NGD 2000-1 in 2003). Ultimately, the future clinical success of C5aR antagonists will depend on their potency under physiologically relevant conditions and robust receptor coverage, safety and tolerability, and the careful choice of appropriate therapeutic indications based on a deep understanding of the biology of C5aR.

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