Controlling the complement system in inflammation

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Abstract

Inappropriate or excessive activation of the complement system can lead to harmful, potentially life-threatening consequences due to severe inflammatory tissue destruction. These consequences are clinically manifested in various disorders, including septic shock, multiple organ failure and hyperacute graft rejection. Genetic complement deficiencies or complement depletion have been proven to be beneficial in reducing tissue injury in a number of animal models of severe complement-dependent inflammation. It is therefore believed that therapeutic inhibition of complement is likely to arrest the process of certain diseases. Attempts to efficiently inhibit complement include the application of endogenous soluble complement inhibitors (C1-inhibitor, recombinant soluble complement receptor 1 - rsCR1), the administration of antibodies, either blocking key proteins of the cascade reaction (e.g. C3, C5), neutralizing the action of the complement-derived anaphylatoxin C5a, or interfering with complement receptor 3 (CR3, CD18/11b)-mediated adhesion of inflammatory cells to the vascular endothelium. In addition, incorporation of membrane-bound complement regulators (DAF-CD55, MCP-CD46, CD59) has become possible by transfection of the correspondent cDNA into xenogeneic cells. Thereby, protection against complement-mediated inflammatory tissue damage could be achieved in various animal models of sepsis, myocardial as well as intestinal ischemia/reperfusion injury, adult respiratory distress syndrome, nephritis and graft rejection. Supported by results from first clinical trials, complement inhibition appears to be a suitable therapeutic approach to control inflammation. Current strategies to specifically inhibit complement in inflammation have been discussed at a recent meeting on the 'Immune Consequences of Trauma, Shock and Sepsis', held from March 4–8, 1997, in Munich, Germany. The Congress (chairman: E. Faist, Munich, Germany), which was held in close cooperation with various national and international shock and trauma societies, was attended by about 2000 delegates from 40 countries. The major objective of the meeting was to provide an overview on the most state-of-the-art methods to prevent multiple organ dysfunction syndrome (MODS)/multiple organ failure (MOF) following the systemic inflammatory response (SIRS) to severe trauma. One of the largest symposia held within the Congress was devoted to current aspects of controlling complement in inflammation (for abstracts see: Shock 1997, 7 Suppl., 71–75). After providing the audience with information on the scientific background by addressing the clinical relevance of complement activation (G.O. Till, Ann Arbor, MI, USA) and discussing recent developments in modern...
complement diagnosis (J. Köhl, Hannover, Germany), B.P. Morgan (Cardiff, UK) introduced the symposium’s special issue by giving an overview on complement regulatory molecules. Selected topics included overviews on the application of C1 inhibitor (C.E. Hack, Amsterdam, NL), sCR1 (U.S. Ryan, Needham, MA, USA), antibodies to C5 (Y. Wang, New Haven CT, USA) and to the anaphylotoxin C5a (M. Oppermann, Göttingen, Germany), and a report on complement inhibition in cardiopulmonary bypass (T.E. Mollnes, Bodø, Norway). The growing interest of clinicians in complement-directed anti-inflammatory therapy, and the fact that only some of the various aspects of therapeutic complement inhibition could be addressed on the meeting, has motivated the author to expand a Congress report into a short comprehensive review on recent strategies to control complement in inflammation. © 1997 Elsevier Science B.V.

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1. **Introduction**

The complement system (for review see Müller-Eberhard, 1988; Rother and Till, 1988) provides a rapid and efficient means to protect the host from invasive microorganisms. Due to its diverse biological activities, complement is a key mediator of inflammation, a natural response of the host tissue to any injury. There is also increasing evidence that complement significantly contributes to the regulation of the immune response (Carroll and Fischer, 1997).

The complement system consists of about 30 proteins, acting within a cascade-like reaction sequence (Fig. 1), serving as control proteins (Fig. 2) or as cellular receptors. Complement can be activated by any of three pathways, either the antibody-dependent classical pathway, the alternative pathway, or the recently discovered MBL/MASP (mannan binding lectin/MBL-associated serine protease) pathway (Turner, 1996). Following complement activation, proinflammatory peptides like the anaphylatoxins C3a and C5a are generated and the membrane attack complex, C5b-9, is formed. Complement activation products, especially the anaphylatoxins, elicit a number of biological effects such as chemotaxis of leukocytes, degranulation of phagocytic cells, mast cells and basophils, smooth muscle contraction and the increase of vascular permeability (Hugli, 1986). In addition, generation of toxic oxygen radicals and the induction of synthesis and release of arachidonic acid metabolites and cytokines lead to the amplification of the inflammatory response. Thus, effector functions arising from complement activation carry the potential for harming the host by directly and indirectly mediating inflammatory tissue destruction.

Under physiological conditions uncontrolled activation of complement is prevented by a vast array of regulatory proteins, either circulating in the plasma,
or expressed on the cell surface (Fig. 2). Host cells are protected against the deleterious attack of homologous complement by the complement receptor 1 (CR1, CD35), the membrane cofactor protein (MCP, CD46) and by glycosylphosphatidylinositol (GPI)-anchored proteins such as the decay-accelerating factor (DAF, CD55), the C8-binding protein/homologous restriction factor (C8bp/HRF) and CD59 (Devine, 1991).

Considerable clinical and experimental evidence implicate the role of complement in the pathogenesis of numerous inflammatory diseases (for review see Dalmasso, 1986; Morgan, 1990). These include not only immune complex and autoimmune disorders, but also organ failure subsequent to sepsis, multiple trauma and burns. The pivotal role of complement to a wide spectrum of diseases has been underlined by the study of genetic deficiencies (Rother and Rother, 1986) and the design and exploration of experimental disease models.

In recent years great advances have been made in the use of complement measurements for the diagnosis and assessment of disease severity, evolution and response to therapy. Complement analysis has also been shown to be of prognostic value in early recognition of patients at risk to develop multiple organ failure after trauma (Zilow et al., 1990) or with empeding a graft rejection following renal transplantation (Kirschfink et al., 1992). Modern diagnostic technologies which focus on the quantification of complement-derived split products or protein–protein complexes provide a comprehensive insight into the activation state of the system (Cooper et al., 1983; Kirschfink, 1997). In his overview, Koehl (Hannover, Germany) focused on recent developments in complement diagnosis, demonstrating that by applying a combination of affinity chromatography with immuno-assay procedures plasma concentrations of anaphylatoxins can now be assessed within 20–30 min. This method fulfills the prerequisite for the introduction of complement analysis in intensive care units (Hartmann et al., 1993). Applying this novel assay to a recent polytrauma study (Hecke et al., 1997) and in patients with sepsis or SIRS (Stöve et al., 1996) it was demonstrated that C3a plasma levels correlated with the clinical outcome and helped to distinguish between patients with sepsis and those with SIRS.

2. Complement depletion by cobra venom factor

Cobra venom factor (CVF), a non-toxic protein in cobra venom, forms a stable bimolecular C3/C5 convertase (Fritzinger et al., 1994), which subsequently leads to unrestricted complement consumption. For many years, complement depletion by CVF provided the only experimental means to analyse the significance of complement to inflammation (Cochrane et al., 1970). As a ‘gold standard’, CVF is still used to comparatively evaluate the efficacy of most inhibitory molecules described in this overview. However, despite its capacity to exert significant protection in complement-mediated pulmonary injury (Ren et al., 1994; Dehring et al., 1987), experimental allergic neuritis (Vriesendorp et al., 1995), vasculitis (Mathieson et al., 1994) and hyperacute xenograft rejection (Gewurz et al., 1967; Chrupcala et al., 1994; Azimzadeh et al., 1996) the strong immunogenicity of purified CVF has hitherto precluded its clinical application. The molecule has been cloned by Fritzinger et al. (1994) and modified recombinant forms of CVF may be generated which may become valuable for medical therapy.

3. Influence of synthetic compounds on complement

A variety of synthetic compounds have been tested for their impact on the complement system. For example, 6-amidino-2-naphthyl-4-guanidinobenzoate (FUT-175), a synthetic serine proteinase inhibitor, was shown to also be a potent inhibitor of C1s, factor D and of C3/C5-convertase activity (Inagi et al., 1991). FUT-175 was successfully tested in animal experiments of discordant xenotransplantation (Kobayashi et al., 1996), acute experimental pancreatitis (Araida et al., 1995) and myocardial ischemia/reperfusion injury (Homeister and Lucchesi, 1994). Upon administration of FUT-175 to glomerulonephritic patients with hypocomplementemia, serum complement levels improved and proteinuria was significantly reduced (Fujita et al., 1993). In a clinical trial on subarachnoid hemorrhage, FUT-175 significantly reduced the incidence of cerebral infarction (Yanamoto et al., 1992). However, it is not clear yet what the relative contribution...
of complement inhibition is to an improvement of the clinical outcome.

The sulfonated dextran polymer (CMDBS25) interferes with the assembly of the classical and alternative C3 convertases (Crepon et al., 1987). In a previous animal experiment the dextran derivative was shown to exhibit potent inhibitory activity towards complement activation in vivo (Thomas et al., 1995). In an in vitro model of hyperacute xenograft rejection porcine endothelial cells were protected against the deleterious attack of human complement (Thomas et al., 1996).

In general, most of the known synthetic complement inhibitors are either toxic, not complement-specific, or require unrealistically high concentrations to inhibit complement in vivo (Asghar, 1984).

4. Immunoglobulins as a scavenger for activated complement

The intravenous application of immunoglobulin (IVIG) has been used as a therapy in various diseases, some of them known to be based on type II hypersensitivity reactions induced by antibody and complement (Mouthon et al., 1996). Supraphysiological doses of Ig have been shown to significantly increase the survival rate in experimental Forssman shock (Basta et al., 1989) and to prevent hyperacute rejection of porcine hearts transplanted into nonhuman primates (Magee et al., 1995). It appears that Ig in high concentration acts as a scavenger for activated C3 and C4, thereby preventing the cascade reaction from taking place on the host tissue. The inhibitory activity appears to be most pronounced in a mixture of Igs of different isotypes (Miletic et al., 1996). High-dose intravenous Ig has been shown to be beneficial in patients suffering from dermatomyositis. Immunohistochemical analysis revealed a significantly reduced deposition of C3b and C5b-9 in endomysial capillaries (Basta and Dalakas, 1994). According to Lutz et al. (1996), high dose IgG not only displaces C3b from its target, but also augments factor I-dependent inactivation of C3b-IgG complexes in vivo, thereby attenuating complement activation via the amplification loop. There is increasing evidence that rapid clinical improvement in patients with systemic vasculitis (Gross, 1994), Kawasaki syndrome (Newburger et al., 1986) or the bullous pemphigoid (Stiehm et al., 1987) may at least in part be due to the complement modulatory effect of high doses of immunoglobulin.

5. Support of physiologic complement regulation

Due to their high specificity and the absence of toxic side effects, the introduction of endogenous complement inhibitors appears to be a logical approach to blocking the complement system in vivo.

C1-inhibitor is a member of the superfamily of serine protease inhibitors (serpins, Carrell and Boswell, 1986). It is a major regulator of complement (C1r, C1s) as well as of the contact phase of coagulation (factor XI, factor XII) and of kallikrein, thus controlling the generation of kinin-like molecules (Schapira et al., 1985).

Based on the hypothesis that in sepsis a relative deficiency of C1-inhibitor might contribute to the development of fatal complications, substitution with this regulatory protein has been found to be of advantage for the clinical outcome. Hack (Amsterdam, Netherlands) summarized the development of C1-inhibitor therapy from its primary indication as an acute treatment in hereditary angioedema (Gadek et al., 1980; Bork and Witzke, 1988) to its application in cases of fulminant inflammation. High doses of C1-inhibitor were safely administered to patients with septic shock, or in cases of capillary leak syndrome associated with IL-2 therapy and this led to attenuation of complement system activation (Hack et al., 1993). C1-inhibitor concentrate has also been applied successfully in capillary leak syndrome after bone marrow transplantation (Nürnberg and Göbel, 1996) as reported by Nürnberg (Düsseldorf, Germany). Administration of C1-inhibitor to children undergoing open-heart surgery, who developed the capillary leak syndrome associated with IL-2 therapy and this led to attenuation of complement system activation (Hack et al., 1993). C1-inhibitor concentrate has also been applied successfully in capillary leak syndrome after bone marrow transplantation (Nürnberg and Göbel, 1996) as reported by Nürnberg (Düsseldorf, Germany). Administration of C1-inhibitor to children undergoing open-heart surgery, who developed the capillary leak syndrome, substantially improved clinical, hemodynamic and respiratory parameters (Stieh et al., 1996). A cardioprotective effect of C1-inhibitor was observed in a cat model of myocardial ischemia and reperfusion (Buerke et al., 1995) and was effective in animal models of endotoxin-induced organ dysfunction (Guerrero et al., 1993) and burn injury (Radke et al., 1995). Recent data from a clinical study in burn patients suggest a favorable
effect of C1-inhibitor treatment (A. Janssen, Mar-
burg, Germany). The expanding field of clinical
indications for C1-inhibitor therapy has recently been
discussed in a workshop held in Düsseldorf, Ger-
many, 1996 (for overview see: Biomedical Progress,
9, Suppl. 1, 1996). Although the impact of C1-inhibi-
tor on complement is restricted to the classical path-
way, its regulatory function in the coagulation sys-

tem offers certain advantages in situations such as
septic shock where activation of either system is
associated with a poor clinical outcome (Nuijens et
al., 1988).

**Complement receptor 1** (CR1, CD35) is a single-
chain membrane-bound glycoprotein with a dual
function. It mediates phagocytosis of C3b-opsonized
targets and serves as a potent regulator of C3 and C5
activation (Fearon, 1979). CR1 binds C3b and C4b,
exerts cofactor activity for factor-I mediated prote-
olytic degradation of these molecules and accelerates
the decay of both the classical and the alternative
C3/C5 convertases. The extramembraneous part of
CR1 was isolated from plasma and shown to retain
full regulatory activity. A truncated soluble molecule,
lacking the transmembrane and cytoplasmic domains
was prepared from CHO cells transfected with a
modified CR1 cDNA (Weisman et al., 1990). The
recombinant soluble complement receptor 1 (sCR1)
inhibits both the alternative and classical pathway
activation in whole serum in a nanomolar concentra-
tion range and was found to be 100-fold more effec-
tive than the endogenous C3/C5 convertase in-
hibitors C4bp and factor H (Fearon, 1991). Serving
as a cofactor for the serum protease factor I, sCR1
further promotes the degradation of C3b and C4b to
inactive forms which no longer bind to sCR1, releas-
ing the regulator to recycle in the inactivation pro-
cess.

U.S. Ryan (Needham, MA, USA) reviewed the
abundant data on the application of sCR1 in various
animal models of inflammatory diseases. After pro-
ving that sCR1 is well tolerated by humans, phase II
clinical trials are currently in progress to evaluate its
therapeutical potential in patients with established
adult respiratory distress syndrome, myocardial in-
farction and to prove its efficacy in reperfusion
injury subsequent to lung transplantation.

In numerous animal models, the application of
sCR1 significantly reduced complement-mediated
tissue damage, as shown for myocardial (Weisman
et al., 1990; Homeister and Lucchesi, 1994), intestinal
(Hill et al., 1992) and hepatic (Jaeschke et al., 1993;
Chavez Cartaya et al., 1995) ischemia/reperfusion
injury. Benefical effects of sCR1 treatment were also
reported for reverse passive Arthus reaction (Yeh
et al., 1991), ARDS (Rabenovici et al., 1992), comple-
ment-mediated experimental glomerulonephritis
(Couser et al., 1995) and demyelinating experimental
allergic encephalitis (Piddlesden et al., 1994).

Despite its rare occurrence, hyperacute graft rejec-
tion, which is mediated by the action of natural
antibodies and complement, is a significant problem
in transplantation surgery. In addition, it represents
the major barrier to xenotransplantation, which is
frequently discussed as a potential solution to the
shortage of human donor organs (Platt and Bach,

In several models of allogeneic and xenogeneic
organ transplantation it could be demonstrated that
pretreatment of the recipient with sCR1 significantly
prolonged survival of heart (Pruitt and Bollinger,
1991) and kidney (Chrupcala et al., 1994) trans-
plants.

The problem of a rapid clearance of therapeutic
reagents like sCR1 from the blood may be solved by
creating chimeric proteins of the inhibitory molecules
and other proteins having longer half-lives, such as
immunoglobulins (Kalli et al., 1991).

A simultaneous inhibition of complement and cell
adhesion was suggested by U.S. Ryan (Needham) to
improve anti-inflammatory therapy. The incorpora-
tion into sCR1 of the seLe φ oligosaccharide, the
common carbohydrate ligand for the P-, E- and
L-selectin adhesion molecules, would allow the com-
bined inhibition of complement activation and se-
lectin-mediated cellular interaction.

In order to overcome complement-mediated hy-
peracute rejection of discordant xenografts (for re-
view see: Dalmasso, 1992) human **membrane-assos-
ciated regulatory proteins** have been transferred onto
xenogeneic tissue. Dalmasso et al. (1991) were able
to demonstrate that human DAF can be directly
inserted by its GPI-anchor into porcine endothelial
cell membranes, thereby preventing lysis of the cells
by human complement. Subsequently, protection of
xenogeneic cells was achieved by transfection with
cDNA of human MCP, DAF or CD59. In a recent
series of experiments we demonstrated that transfection of porcine endothelial cells with human CD59 by itself or in combination with soluble regulators effectively inhibited cell destruction by human serum complement (Heckl-Östreicher et al., 1996). Kooyman et al. (1995) were able to show that GPI-linked complement regulatory proteins expressed on the surface of transgenic mouse or pig erythrocytes can be transferred in an active form to vascular endothelium in vivo. A major step forward towards the clinical application of xenotransplantation was the generation of transgenic donor animals that express human complement inhibitor proteins on their tissue (Cozzi and White, 1995; Byrne et al., 1996; Kroshus et al., 1996). Quantitative analysis of the human regulator DAF in different pig organs displayed an expression level which was comparable or even higher than on normal human endothelium (Langford et al., 1994). Morphologic and functional analysis revealed that in xenoperfused hDAF/hCD59 transgenic pig hearts (Schmoeckel et al., 1996; Kroshus et al., 1996; Byrne et al., 1997) and kidneys (Storck et al., 1997) the human regulators were sufficiently expressed to inhibit complement activation and to significantly reduce morphologic alterations indicative of hyperacute graft rejection.

6. Blocking complement components

By inhibition of the complement cascade reaction at C5, the formation of the membrane attack complex is blocked and the generation of the proinflammatory peptide C5a is abolished. Y. Wang (New Haven, CT, USA) presented two murine preclinical models of systemic lupus erythematosus and rheumatoid arthritis. Treatment with monoclonal anti-C5 antibodies resulted in a marked amelioration of the course of renal disease (Wang et al., 1996) and of joint inflammation (Wang et al., 1995), respectively. For clinical application, from the monoclonal antibody N19-8, developed and characterized by Würzner et al. (1991), a humanized single chain anti-C5 antibody (h5G1.1scFv) has been constructed (Evans et al., 1995) and shown to be a potent inhibitor of complement as well as of platelet and leukocyte activation in an in vitro model of extracorporeal circulation relevant to cardiopulmonary bypass (CPB). Pharmacokinetic and pharmacodynamic data from a phase I clinical trial indicate that a single bolus of the humanized anti-C5 scFv may sufficiently block complement activation during CPB (Rollins et al., 1997). Anti-C5 scFv may also provide an alternative approach to the treatment of immune complex mediated tissue inflammation. In previous experiments, Rollins et al. (1995) demonstrated that by the addition of monoclonal anti-C5 and anti-C8 IgG isolated rat hearts perfused with human serum were protected against complement-mediated organ damage. Addition of anti-C5 IgG to human blood used to perfuse porcine hearts ex vivo prevented acute tissue injury (Kroshus et al., 1995). Administration of various monoclonal antibodies against rat C3 led to increased survival time of guinea pig hearts transplanted into rats (Kemp et al., 1994).

7. Inhibition of the anaphylatoxin C5a

With respect to its diverse biological functions, the complement-derived anaphylatoxin C5a is considered to be one of the most potent phlogistic peptides (Hugli, 1986). Inflammatory cells react to nanomolar concentrations of C5a with chemotaxis, upregulation of adhesion molecules and the release of destructive oxygen radicals and lysosomal pro- teases. Mice, defective in C5 and thereby unable to generate C5a upon complement activation, have been shown to be protected in septic shock (Hsueh et al., 1990). M. Oppermann (Gottingen, Germany) summarized current data on anti-C5a treatment, pointing to conflicting results from different animal studies. In two models of septic shock, by the prophylactic administration of anti-C5a antibodies, the mortality rate was significantly reduced and the animals showed a considerable improvement of their hemodynamic condition (Stevens et al., 1986; Smedegard et al., 1989). In contrast, monoclonal antibodies directed against a porcine C5a/C5adesArg neoepitope had no beneficial effect on mortality and organ function in a pig septic model. However, upon anti-C5a treatment, significantly less 11-6 was generated, supporting the notion of an immunoregulatory role of C5a (Höpken et al., 1996). As outlined by G.O. Till (Ann Arbor, MI, USA), anti-rat C5a efficiently blocked complement (C5a)-mediated upregulation of
8. Interference with leukocyte adhesion

The complement receptors CR3 and CR4 (CD18/CD11b,c), members of the β2 integrin family, promote adhesive interactions of leukocytes with the vascular endothelium. As an 'experiment of nature' the leukocyte adhesion deficiency syndrome (LAD), caused by an inherited deficiency of the leukocyte β2 integrin receptor CD11/CD18 in man (Harlan, 1993) and cattle (Kehrli et al., 1990), has provided important insights into the molecular basis of leukocyte recruitment from the circulation to extravascular sites of inflammation. Adhesion molecules are recognized as key determinants of the inflammatory response (Mulligan et al., 1993a,b) and have therefore gained considerable interest as targets of antiphlogistic therapy.

The role of β2 integrins in lung injury has been determined by the application of blocking antibodies. Anti-CD18 and anti-CD11b antibodies reduced complement-mediated lung injury either induced by CVF or by immune complexes (Mulligan et al., 1993a,b). Early treatment with anti-CD11b also substantially increased survival of rats with experimental allergic encephalitis (Huisinga et al., 1993) and protected dogs from myocardial reperfusion injury (Simpson et al., 1988). Furthermore, monoclonal antibodies directed against CD18 were shown to reduce vascular rejection in a rabbit heterotopic heart transplant model (Sadahiro et al., 1993).

9. Complement inhibition on blood-interacting biomaterials

The inflammatory response induced by artificial surfaces in hemodialysis and extracorporeal circuits may lead to organ dysfunction. Complement activation has been shown to be associated with transient neutropenia, pulmonary vascular leukostasis and occasionally anaphylactic shock of varied severity in patients undergoing hemodialysis (Johnson, 1994) or cardiopulmonary bypass (Chenoweth, 1986; Gardi-
Fig. 3. Therapeutic control of the complement reaction may be possible by the application of physiological regulatory proteins, the administration of blocking antibodies, or, with respect to xenotransplantation, by genetransfer (e.g. CD59\textsubscript{g}). C5aR\textsubscript{An}tag., C5a receptor antagonist.

Biomedical polymers considerably differ in their capacity to activate complement (Janatova et al., 1991). It is therefore accepted that evaluation of biocompatibility of artificial surfaces has to include the analysis of activation of both the coagulation and complement systems (Cheung, 1994; Mollnes et al., 1995). Heparin with its well-known anticoagulatory effect is also considered a potent inhibitor of the complement system, especially if it is bound to the surface of an activator (Cheung et al., 1992; Edens et al., 1993). Mollnes (Bodø, Norway) summarized data on the substantial improvement of biocompatibility of CPB devices upon end-point attachment of heparin to the surfaces of an extracorporeal circuit as tested in animal experiments and in vitro with human blood in closed circuits (Kirschfink et al., 1993; Redmond et al., 1993; Mollnes, 1997).

A recent clinical study with patients randomized to operation with either uncoated or heparin-coated surfaces demonstrated a significant reduction of complement activation accompanied by an attenuation of the leukocyte integrin and selectin response (Moen et al., 1997). Alternatively or in addition, complement activation by CPB devices may be reduced by the application of anti-C5 scFv (Rollins et al., 1997) or sCR1 (Gillinov et al., 1993)

10. Conclusion

Stimulated by promising results from experimental and first clinical studies (Table 1), research institutions and industry are pursuing strategies to inhibit complement activation as a novel therapeutic approach for many inflammatory diseases. Furthermore, effective complement inhibition may provide an avenue for successful xenotransplantation. However, drug designers and clinicians must take into consideration that the effective systemic inhibition of complement will deprive the patient of an important immunological defense system.

Double-blinded controlled clinical trials are needed to definitively prove the therapeutic potential of targeted complement inhibition (Fig. 3) to reduce morbidity and mortality.

References


Basta, M., Dalakas, M.C., 1994. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermat-
Gewurz, H., Clark, D.S., Cooper, M.D., Varco, R., Good, R.A.,


Kroshus, T.J., Bolman, R.M. III, Dalmasso, A.P., Rollins, S.A.,


effect of cobra venom factor on pulmonary injury induced by oleic acid. Int. J. Immunopharmacol. 16, 969–975.


