17.7.2 Other Potential Clinical Indications

Interest is increasing in exploring the clinical use of C1-inhibitor in other clinical settings [55, 119, 120]. This is not only based on the fact that C1-inhibitor downregulates the complement and contact activation systems but also on its strong anti-inflammatory properties that appear to be independent of its protease targeting function [49, 55, 121–123]. The anti-inflammatory activity seems to be exerted by the heavily glycosylated N-terminal domain of the molecule [124, 125] and involves noncovalent interactions with proteins (extracellular matrices), cells, bacteria, and endotoxins. The following is a brief and nonexhaustive summary of recent findings from animal models and preliminary studies in man.

1.*Sepsis and Endotoxemia*. These clinical conditions lead to activation of both the complement and contact system, which, when excessive, may result in pathologic inflammation and shock. Sepsis has also been shown to generate inactive C1-inhibitor in the circulation [25]. Therefore, it has been speculated that administration of C1-inhibitor in these conditions could have a beneficial effect.

In sepsis, positive outcomes have been reported in animal models, including baboons [126] and mice and rats [127, 128]. This has prompted a number of preliminary trials in humans [129–133] that have shown favorable results.

In endotoxemia, studies on endotoxin-induced shock displayed encouraging results in dogs [134], mice [135], and man [136]. In addition to inhibiting the inflammatory activated complement, the anti-inflammatory effect is also ascribed to binding of endotoxin to the N-terminal portion of the C1-inhibitor protein [124, 125, 135].

2. Treatment of *Capillary Leak Syndrome* (CLS) with C1-inhibitor has also been tested. It has been reported that administration of C1-inhibitor, in a pilot study of six patients, markedly decreased the side effects of treatment with interleukin 2 [137]. Promising results were observed in a group of 15 patients with CLS following bone marrow transplantation and in two patients with CLS after lung transplantation when transfused with C1-inhibitor. A similar result was observed in a case of severe CLS after stem cell transplantation that was treated with a combination of C1-inhibitor and plasminogen activator [138–140]. Furthermore, in a randomized double-blind trial in 24 neonates undergoing cardiac surgery with cardiopulmonary bypass, results indicated that prophylactic therapy with C1-inhibitor resulted in less inflammatory responses and capillary leak than in the placebo group [141]. It should be noted that a year earlier fatal thromboembolic complications had been observed in a similar patient group, following use of very high dosages of C1-inhibitor (500 PU/kg) in an attempt to prevent CLS [142]. In the above study, the C1-inhbitor was administered at a dose of 100 PU/kg.

3.*Ischemia and Reperfusion Injury*. Acute myocardial infarction is associated with local inflammatory reactions, due to activation of the contact system and complement system. In animal models of myocardial infarction beneficial effects have been shown in rats [143], pigs [144], cats [145], and mice [56]. Studies of myocardial and brain infarction in humans have also shown favorable results [146–152]. Other studies involving the examination of the effect of C1-inhibitor in liver ischemia in the rat [153], *ex vivo* reperfusion of pig liver [154], ischemia and reperfusion injury of skeletal muscles in mice [155], intestinal ischemia in a mouse model [156], and a number of animal models of transplantation [157–160] have generated promising results with respect to the possible application in human clinical conditions. There are also indications that C1-inhibitor therapy is capable of inhibiting antibody-mediated organ transplant rejection, as studied in primates [161, 162].

4.*Pancreatitis*. Several publications describe a beneficial effect of administering C1-inhibitor in animal models of acute pancreatitis [163, 164] and in humans [165–167], although in some other animal studies this effect was not confirmed [168].

5. Positive outcomes have been reported for a number of other animal models relating to burns [169, 170], thermal injury [171], and trauma [172].

A relatively new development is the potential use of C1-inhibitor in fibrinolytic treatment, where it was shown *in vitro* and in a dog model that nonspecific plasminogen activation could be counteracted by C1-inhibitor, allowing higher and hence more effective doses of a recombinant prourokinase mutant [173, 174]. Also, positive results of C1-inhibitor use in a mouse model for malaria were announced recently [56]. A comprehensive review of possible novel applications of C1-inhibitor has recently been published [175].

17.8 Future Trends

A clear trend over the past few years in the treatment of HAE has been the use of C1-inhibitor in prophylactic regimens, and even treatment at home. Clinical experience has clearly shown that C1-inhibitor is safe and effective when used prophylactically and this represents a major step forward in the treatment of this potentially life-threatening disease [113, 114, 176, 177]. As with almost every other human plasma-derived therapeutic there are some developments that will have an impact on the production and clinical usage of plasma-derived C1-inhibitor. First of all, C1-inhibitor can be produced via recombinant-DNA technology, such as in transformed COS cells, Chinese hamster ovary (CHO) cells, and yeast (*Pichia pastoris*) [178–180]. At this point, the only recombinant C1-inhibitor product that has been investigated in HAE patients has been produced transgenically [181, 182]. This product, called conestat alpha, is extracted from the milk of transgenic rabbits and is produced by Pharming NV, The Netherlands (trade names in Europe and United States are Ruconest® and Rhucin®, respectively). Its glycosylation differs from the human plasma-