Respiratory Medicine (2015) 109, 758–767

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Concept for a study design in patients with severe community-acquired pneumonia: A randomised controlled trial with a novel IGM-enriched immunoglobulin preparation — The CIGMA study

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Received 4 September 2014; accepted 23 March 2015
Available online 2 April 2015

Abbreviations: ATC, anatomical therapeutical chemical; APC, activated protein C; ATS, American Thoracic Society; CAP, community-acquired pneumonia; CI, confidence interval; CRO, Clinical Research Organisation; DSMB, Data Safety Monitoring Board; ICU, intensive care unit; IDSA, Infectious Disease Society of America; IVIG, intravenous immunoglobulin; PEEP, positive end-expiratory pressure; PI, probabilistic index; RR, relative risk; rTFPI, recombinant tissue factor pathway inhibitor; SBT, spontaneous breathing trial; sCAP, severe community-acquired pneumonia; SOFA, Sequential Organ Failure Assessment (score); SD, standard deviation; TLR4, toll-like receptor 4; VFD, ventilator-free day; WBC, white blood cell.

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http://dx.doi.org/10.1016/j.rmed.2015.03.008

KEYWORDS
Severe community-acquired pneumonia;
IgM-enriched immunoglobulins;
Mechanically-ventilated;
Adjunctive therapy;
Ventilator-free days;
BT086

Summary
Introduction: Severe community-acquired pneumonia is defined as community-acquired pneumonia that requires intensive medical care. Mortality in these patients is still high depending on time and admission. Since bad outcomes may occur despite antibiotic therapy to treat severe community-acquired pneumonia, the focus has shifted to targeting the host response. The CIGMA Study examines the safety and efficacy of the novel IgM-enriched immunoglobulin preparation BT086 when added to standard of care treatment.
Methods/design: The aim of this multicentre, randomised, placebo-controlled, double-blind, parallel-group, adaptive group-sequential phase II study is to determine the efficacy and safety of BT086, an IgM-enriched immunoglobulin preparation, as an adjunctive treatment in mechanically-ventilated patients with severe community-acquired pneumonia. The increase of ventilator-free days is the primary endpoint in this study. For this trial, ventilator-free days are defined as the number of days between successful extubation from endotracheal ventilation and day 28 after enrolment of the patient into the study. Two interim analyses were considered for this study.
Discussion: Several novel agents for treatment of sepsis have been evaluated in the last two decades; however, none has significantly reduced mortality rates. Failure was attributed to the heterogeneity of septic patients or sepsis. Severe community-acquired pneumonia was chosen as the indication for this study to increase homogeneity within this patient population.
Trial registration: EUDRACT 2010-022380-35.

Introduction

The CIGMA (Concentrated IgM for Application) Study is a multicentre, multi-national, randomised, placebo-controlled, parallel-group, adaptive group-sequential phase II study to determine the efficacy and safety of the IgM-enriched immunoglobulin preparation BT086 as an adjunctive treatment in severe community-acquired pneumonia (sCAP).

Community-acquired pneumonia (CAP) occurring in individuals who have not recently been in hospital is a significant cause of morbidity and mortality in adults. CAP mortality rates are high and have not changed significantly over the past several decades despite the availability of improved broad-spectrum antibiotics [1,2]. CAP incidence varies by geographic region, gender (more common in men than in women), and age (more common in people aged $\geq$65 years). Mortality has been reported to vary from $<$1% to 48% and is associated with advanced age, co-morbid conditions, and CAP severity [3]. In the United States, CAP is the number one cause of death from infectious diseases and the eighth leading cause of death, with an estimated 1.3 million hospitalisations each year and an estimated cost of $40 billion [4].

sCAP is usually defined clinically as CAP that requires intensive medical care. Up to 10% of hospitalized adult CAP patients require intensive medical care and are transferred to intensive care units (ICUs) [5] with great impact on health care costs [3,6] and outcome. Mortality of sCAP patients admitted to ICUs usually ranges from 35 to 58% depending on time and admission to hospital [7]. However, two recent trials on sCAP found a mortality rate of only 17.9% [8] and 23.1% [9].

A review published by Cillóniz et al. [10] reported that the aetiology for CAP was unknown in more than 50% of cases despite the use of ever improving microbiological techniques. The most common identified cause of CAP and sCAP remains the bacterium *Streptococcus pneumoniae* [3,10].

Widespread increased resistance of common respiratory pathogens to antibiotics is becoming a major challenge in treating this life-threatening condition [3,11].

Since bad outcomes may occur despite antibiotic therapy in sCAP, attention has turned to targeting the host response in an attempt to improve sCAP outcomes. This approach is supported by the observation that systemic cytokine response to pathogens leads to the progression of sCAP, and the spectrum of circulating cytokines in hospitalised sCAP patients is indicative of elevated inflammation in most cases, irrespective of sepsis [12]. Recombinant tissue factor pathway inhibitors (rTFPI), activated protein C (APC), corticosteroids, and intravenous immunoglobulins have been investigated for their potential as adjunctive and host-targeted treatments for sCAP [2].

The rTFPI tifacogin has been shown to restore regulation of tissue factor pathways, reducing mortality, inflammation, and lung injury in a number of animal models. After promising initial results in small patient populations, a controlled trial (2138 patients) was conducted with tifacogin in adults with sCAP [8]. In this large trial tifacogin treatment had no mortality benefit in patients with sCAP, despite evidence of biological activity as an anticoagulant protein.

APC has antithrombotic, anti-inflammatory, and profibrinolytic properties that might be beneficial in the treatment of sCAP. The PROWESS trial, conducted in 1690 patients with severe sepsis, reported that treatment with APC (drotrecogin alfa activated [Xigris®]) significantly reduced mortality in patients with severe sepsis but may be associated with an increased risk of bleeding [13]. In contrast, the PROWESS SHOCK trial conducted in 1697