Granulocyte colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults

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Granulocyte colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults

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ABSTRACT

Background
Granulocyte colony stimulating factor (G-CSF) is a naturally-occurring cytokine that has been shown to increase neutrophil function and number. Exogenous administration of recombinant G-CSF (filgrastim, pegfilgrastim or lenograstim) has found extensive use in the treatment of febrile neutropaenia, but its role in the treatment of infection in non-neutropaenic hosts is less well defined.

Objectives
We aimed to explore the role of G-CSF as an adjunct to antibiotics in the treatment of pneumonia in non-neutropaenic adults.

Search strategy
A search was performed using the Cochrane Central Register of Controlled Trials (issue 1, 2003); MEDLINE (January 1966 to April 2003); EMBASE (1988 to 2003); online databases of clinical trials; contact with corresponding authors; and contact with the manufacturers and distributors of G-CSF and reviews of citations in publications identified by the above strategies.

Selection criteria
We considered randomised controlled trials (RCTs) which included hospitalised adult patients with either community acquired pneumonia or hospital-acquired pneumonia.

Data collection and analysis
Studies identified were reviewed independently by two reviewers with data abstracted onto standardized data collection forms. The primary outcome measure was 28 day mortality. Secondary outcome measures included other markers of mortality as well as markers of adverse events, including organ dysfunction. An assessment of methodological quality was made for each study.

Main results
G-CSF use appeared to be safe with no increase in the incidence of total serious adverse events (pooled OR 0.91, 95% CI: 0.73, 1.14) or organ dysfunction. However, the use of G-CSF was not associated with improved 28 day mortality (pooled OR 0.99, 95% CI 0.77, 1.29).
Reviewers’ conclusions

There is no current evidence supporting the routine use of G-CSF in the treatment of pneumonia. Studies in which G-CSF is administered prophylactically or earlier in therapy may be of interest.

PLAIN LANGUAGE SUMMARY

Synopsis

Granulocyte colony stimulating factor (G-CSF) does not reduce mortality in adults with pneumonia

Pneumonia, or infection involving the lungs, is responsible for a significant number of deaths worldwide. Pneumonia is especially life-threatening in older people and people with other illnesses that may affect the immune system (such as diabetes). In addition to antibiotics, granulocyte colony stimulating factor (G-CSF) has been suggested as a possible option for treatment. G-CSF stimulates the production of white blood cells that fight infection, and is used for people with cancer after chemotherapy. The review of trials found that G-CSF appears to be a safe treatment for people with pneumonia, but it does not appear to reduce mortality. More research is needed.

BACKGROUND

This review explores the use of granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in non-neutropaenic adults. Much of the mortality associated with pneumonia is related to sepsis, thought to represent a state of uncontrolled inflammation. Immunomodulation of this response, using physiological doses of corticosteroids (Annane 2002 and recombinant activated protein C (Bernard 2001) have been associated with improved outcomes. G-CSF, a naturally occurring cytokine, may augment the neutrophil response to bacterial infections.

Recombinant G-CSF has been shown to increase proliferation and differentiation of neutrophil precursors. It has found widespread use in reducing the duration of febrile neutropaenia following cytotoxic chemotherapy (Weihe 1996), although its effect on mortality is questionable (Berghmans 2002). Other accepted indications include neutropaenia following bone marrow transplantation, the mobilization of peripheral blood progenitor cells in healthy donors and in the treatment of severe congenital neutropaenia.

Its use in non-neutropaenic infection is based on three possible mechanisms of action:

1. enhanced chemotaxis, superoxide production and killing activity (Hartung 1999);
2. immunomodulation of the cytokine response in sepsis (Weiss 1999);
3. a possible increase in intracellular uptake of antibiotics (McKenna 1996).

However, a possible concern with its use in sepsis is the role of neutrophils in the development of organ dysfunction, and in particular adult respiratory distress syndrome (ARDS). Increasing neutrophil number and function may increase the risk of these adverse sequelae. A review of 84 cases of probable G-CSF related pulmonary toxicity, mostly administered following chemotherapy, found that G-CSF may increase the toxicity associated with cytotoxic agents and infectious insults in neutropaenic patients (Azoulay 2001).

G-CSF has shown promise in the treatment of infection in non-neutropaenic hosts in animal models (Hebert 1990; Smith 1995) and in at least one case series with a historical control group (Stephens 2002). It should be distinguished from GM-CSF (sargramostim), which is used occasionally in stem cell mobilization and to promote engraftment following bone marrow transplantation.

Community-acquired pneumonia is the leading cause of death from infectious disease and results in approximately 600,000 admissions per year in the United States (Bartlett 1995). Both community-acquired pneumonia and hospital-acquired pneumonia are associated with a significant mortality. (Fagon 1993a; Niederman 1993). A number of trials of G-CSF in the treatment of pneumonia have been performed. A review of these trials may clarify the role of this immunomodulatory therapy and aid design of future trials.
OBJECTIVES

To assess the effectiveness and safety of G-CSF as an adjunct to antibiotics for the treatment of pneumonia in non-neutropaenic adults.

RESULTS

Mortality and other efficacy endpoints

None of the studies demonstrated a statistically significant mortality benefit; a pooled estimate of efficacy similarly did not demonstrate a significant benefit associated with G-CSF. There was no heterogeneity amongst studies with regard to 28 day mortality (p = 0.14). Pooling results across all four studies, the pooled odds ratio for 28 day mortality was 0.99 (fixed effects model; 95% confidence interval (CI): 0.77, 1.29).

A number of the endpoints intended for analysis were not reported, including time to hospital discharge (no interquartile range reported in any study), the rate of intubation (only reported in Nelson 1998), in-hospital mortality (only reported in Nelson 1998). Duration of ICU stay was not reported in one study (Wunderink 2001).

Adverse events

Overall, there was a reduction in adverse events that was not statistically significant (pooled odds ratio was 0.91; 95% CI: 0.73, 1.14). This was largely due to a reduction in rates in organ dysfunction, highest in the study of community-acquired pneumonia (Nelson 1998). In that study, there was a significant decrease in rates of ARDS (OR 0.28; 95%CI: 0.09, 0.28) but this was not seen in subsequent studies.

Community acquired pneumonia, hospital acquired pneumonia and ventilator-associated pneumonia

Only one of the two studies that included patients with hospital-acquired pneumonia reported results by category. In the larger study (Root 2003), patients with hospital-acquired pneumonia constituted a minority (20%) of patients and were distributed evenly in intervention and placebo groups.

Presence of severe sepsis

Outcome measures were not reported by the presence or absence of severe sepsis in the earlier trials. (Nelson 1998; Nelson 2000). In these trials, however, septic shock was a specific exclusion; the pooled odds ratio of incident septic shock was 0.60 (95%CI: 0.34, 1.08). There was a moderate decrease in 28 day mortality in these trials (pooled OR 0.80; 95%CI: 0.52, 1.22) that was not statistically significant.

There was a trend to an increasing odds ratio of serious adverse events and organ dysfunction in the studies of patients with severe sepsis in filgrastim-treated patients (Wunderink 2001; Root 2003). For total serious adverse events, the pooled odds ratio in the studies of patients with severe sepsis was 1.10 (95%CI 0.82, 1.49) compared to the other studies (0.72 (0.51, 1.01).

Bacterial aetiology

Results were not reported by bacterial aetiology; it was not possible to draw conclusions on the efficacy of G-CSF in each of these groups.

Analyses of patients with specific co-morbidities

We were also unable to perform subgroup analyses on patients with specific co-morbid conditions due to a lack of data.

Sensitivity analysis

Given the small number of studies, all of good quality, no sensitivity analysis was performed.

Assessment of publication bias

No individual study demonstrated a mortality benefit. The ability to interpret a funnel plot was limited by the small number of trials identified.

DISCUSSION

Efficacy

This analysis suggests that there is no clinically significant benefit associated with the use of G-CSF. Richard Root (Root 2003) suggests several reasons for the failure of previous animal work to demonstrate results in humans; invalid hypothesis, inadequate dosing or activity, improper study design or failed execution. He suggests that, primarily, delays in the administration of G-CSF to satisfy microbiological study criteria may have contributed to its negative result.

We performed this review in preparation for a trial of G-CSF in Burkholderiapseudomallei (B. pseudomallei) pneumonia where we wished to determine if G-CSF may benefit patients with acquired neutrophil dysfunction due to co-morbid conditions such as diabetes, alcohol and renal failure, or with infections due to intracellular organisms such as B. pseudomallei. However, we have been unable to answer this question specifically from the data available.

Adverse events

Our results suggest that G-CSF does not increase the rates of immunologically mediated organ dysfunction by a clinically significant extent. A theoretical concern has been that the use of G-CSF may increase the rate of immunologically mediated end-organ dysfunction, such as the adult respiratory distress syndrome (ARDS), to which patients with severe sepsis are particularly prone.

There was a trend towards an increasing risk of organ dysfunction in patients more severely unwell and treated with G-CSF, suggest-
References to studies included in this review

Nelson 1998  {published data only}

Nelson 2000  {published data only}

Root 2003  {published data only}

Wunderink 2001  {published data only}

References to studies excluded from this review

Hustinx 1998

Meyanci 2001

References to studies awaiting assessment

Root 2000
Root RK, Marrie TJ, Lodato RF. Quoted in “A Randomized Controlled Trial of Filgrastim for the Treatment of Hospitalized Patients with Multilobar Pneumonia”. Journal of Infectious Diseases 2000.

Additional references

Annane 2002

ATS Guidelines 1996

Azoulay 2001
Granulocyte colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults (Unknown)

Bartlett 1995

Berghmans 2002

Bernard 2001

Bone 1993

BTS 1987

Clarke 2002

Ewig 1998

Fagon 1993a

Fagon 1993b

Fine 1997

Garner 1988

Hartung 1999

Hebert 1990

McKenna 1996

Niederman 1993

Sanchez-Nieto 1998

Smith 1995

Stephens 2002

Weiss 1999
Welte 1996
* Indicates the major publication for the study

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