The use of macrolides and corticosteroids as immunomodulators in community-acquired pneumonia

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The mortality rate in community-acquired pneumonia (CAP) has remained high. A single episode of pneumonia has an increased mortality rate across all age groups v. controls. Research continues to find ways to decrease the mortality rate associated with pneumonia. Corticosteroids and macrolides have been shown to influence inflammation; their immunomodulatory effect decreases the production of inflammatory cytokines. Their use in CAP is proposed to improve mortality and morbidity. However, controversy over their use has been evident in several trials. Recent trials have shown that beta lactam antibiotic use without a macrolide is non-inferior and that corticosteroid use only confers a mortality benefit in patients requiring ionotropic support. In one study, corticosteroid use reduced hospital stay by 1 day, but had no effect on mortality. The regular use of macrolides and corticosteroids solely as immunomodulators in CAP cannot be advocated at this stage.

S Afr Respir J 2016;22(4):98-101. DOI:10.7196/SARJ.2016.v22i4.45

Despite much advancement in antibiotics and hospital care, mortality from community-acquired pneumonia (CAP) seems to defy all our efforts at reduction. Mortality rates are 12% for CAP without a proven organism and in proven *Streptococcus pneumoniae* infections.[1]

Macrolide antibiotics reduce the activation of nuclear factor kB (NF-kB). NF-kB is responsible for the production of inflammatory cytokines in response to infection, in particular interleukin 8 (IL-8).[2] In addition, they decrease mucus production and reduce cytokine production by the inhibition of pro-inflammatory cytokines (Fig. 1). Macrolides also prevent the formation of biofilm by bacteria, which is an alginate mucoid film that makes the bacteria resistant to antibiotic attack. Biofilms are produced by bacterial signaling (quorum sensing), which macrolides disrupt.[3] Corticosteroids also decrease the transcription of inflammatory cytokines by inhibition of NF-kB.[4] The widespread use of corticosteroids in the control of asthma is a potent example of its anti-inflammatory effect. Could these two agents be of benefit in the acute inflammatory state in CAP, by modifying the host's immune response to prevent unwanted side-effects from inflammation and thereby reducing mortality?

The controversy that surrounds macrolide use in CAP is highlighted by opposing results in several studies.[5]

The macrolide debate

A retrospective cohort study by Restrepo *et al*.[6] showed significant benefits in 30-day and 90-day mortality rates with macrolide use in patients with severe sepsis and pneumonia. However, there was no record of corticosteroid use in patients and the benefit of macrolides to non-intensive care unit (ICU) patients was not evaluated. The same authors, in a later collaborative study selecting *Pseudomonas aeruginosa* as the causative organism in 402 patients from 150 hospitals, against which macrolides have no antibacterial effect, found no effect in mortality by adding a macrolide to the antibiotic regimen.[7] The importance of the study was to isolate the pure immunomodulation effect of macrolides from any possible bacteriostatic or synergistic action with antibiotics in treating pseudomonas infections.

The often-cited meta-analysis by Asadi *et al*.[8] assessed 23 observational cohort studies and 5 randomised controlled trials that showed an overall benefit from macrolide use. However, a macrolide was compared with a non-macrolide antibiotic, and dual therapy of beta lactam and macrolide (BLM) v. beta lactam (BL) alone was not assessed. BLM was only compared with fluoroquinolone (FQ) and showed no added benefit. This meta-analysis favoured the use of a macrolide regimen. However, if the five randomised control trials were considered without the observational cohort studies, the benefit of adding a macrolide was lost, since all the randomised controlled trials showed non-significance.

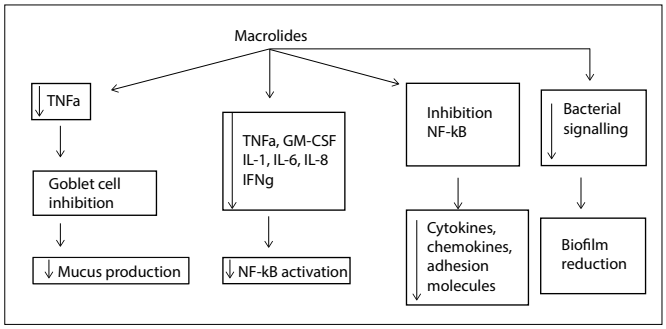

Fig. 1. Function of macrolides. (TNFa = tumour necrosis factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFNg = interferon gamma.)

The meta-analysis conducted by Nie *et al*.[9] involved 4 prospective and 12 retrospective cohort studies. The analysis of all the studies combined showed a clear mortality benefit in favour of macrolide use. However, when the retrospective studies were excluded and only the four prospective studies were analysed, the benefit of macrolide use was lost; three studies showed no benefit, two of which had also included patients in intensive care. The authors acknowledged the need for a randomised control trial to demonstrate the effectiveness of dual therapy with BLM compared with monotherapy with BL.

One such study was the Community Acquired Pneumonia Study on the initial Treatment with Antibiotics of the lower Respiratory Tract infections (CAP-START) trial by Postma *et al*.[10] The investigators examined the effect of BL v. BLM v. FQ. This trial was a cluster randomised study conducted in 4-month blocks and rotated through seven hospitals over 2.5 years. Each hospital used the different treatment regimens according to the Dutch guidelines and all three regimens were rotated every 4 months in each of the seven hospitals. Of the 2 283 patients included in the study, 656 received a BL, 739 received a BLM and 888 received an FQ. The median patient stay was equal in all three antibiotic groups. The 90-day mortality for the BL group was 9.0%, 11.1% for the BLM group and 8.8% for the FQ group, and this difference was not statistically significant. All the patients included in the study were non-ICU admissions. Adverse effects were higher in the BLM group compared with the BL group (7.2% v.1.7%), necessitating a change of antibiotic. The study demonstrated non-inferiority of a BL regimen compared with a BLM regimen.

A caveat to the addition of an antibiotic for pure immunomodulation is the development of resistance by organisms. A study by Malhotra-Kumar *et al*.[11] analysed the resistance of oropharyngeal streptococci that developed after a course azithromycin or clarithromycin. In 74 healthy volunteers there was a 50% increase in resistance to clarithromycin and a 54% increase in resistance to azithromycin. Six months were required for these acquired resistance levels to return to levels prior to antibiotic use.

The high burden of immune-compromised patients created by the HI virus may well negate the possible immunomodulatory effects of macrolides. This may be why HIV seropositive patients were excluded in all trials using macrolides if their CD4 count was <350 cells/μL. Until there is a clear mortality benefit demonstrated by randomised prospective trials using a macrolide, adding a macrolide risks creating increased resistance and hence cannot be recommended as regular additional therapy in CAP for immunomodulation purposes only.

The corticosteroid debate

The use of corticosteroids as immunomodulators in patients with acute respiratory distress syndrome (ARDS) and septic shock from pneumonia is already established.[12] What is not certain is the benefit of the use of steroids for patients with CAP who do not require intensive care management. In these circumstances, the effect of steroids as immunomodulators is tested outside the arena of shock and ARDS.

The use of steroids was so successful in oxygenation improvement in a study by Confalonieri *et al*.[13] that the study was stopped prematurely.

In this study of 46 patients, one of the following major criteria was required for inclusion: patient requiring mechanical ventilation, chest X-ray appearance worsening by 50% or more, or vasopressor use of longer than 4 hours' duration. Two of the following minor criteria were required: a PaO_2/FiO_2 (PF ratio) of <250 mmHg, systolic blood pressure <90 mmHg, bilateral involvement, a respiratory rate >30 breaths/minute or a diastolic blood pressure <60 mmHg. Forty-five of the 46 patients had a PF ratio of <250 mmHg. According to the Berlin criteria[14] for ARDS, a PF ratio of <250 mmHg is already classified as mild ARDS. Fifty-seven percent of the placebo arm had a PF ratio of <200 mmHg. This study was, effectively, a demonstration of the efficacy of steroids in ARDS secondary to CAP rather than in uncomplicated CAP.

A recent double blind randomised controlled trial (RCT) showed that the use of adjunct corticosteroids in CAP led to an earlier time to stability by 1 day, 1 day less of intravenous antibiotics and, consequently, a 1-day earlier discharge from hospital.[15] The time benefit of 1 day could amount to a large cost saving across hundreds of thousands of admissions. There was no mortality benefit from use of corticosteroids in the 800 patients in the study. Those who had active tuberculosis and who were HIV seropositive with a CD4 count of <350 cells/μL were excluded from the trial. The Pneumonia Severity Index (PSI) score grades into five classes and is equivalent to the CURB-65 score, which rates from 1 to 5. Of note in this study by Blum *et al.*[15] was that only 40% of patients in the placebo arm had a PSI category of 3 or less. Fifty-two percent of the patients in the placebo arm were in the two most-ill categories, both requiring ICU care. Of these, 38% were PSI class IV (CURB-65 score 4) and 14% were PSI class V (CURB-65 score 5). There was also an equivalent proportion (47%) of very sick patients in the corticosteroid arm. Therefore, it was difficult to measure which patients benefited the most from steroid use – those who were more severely ill or those in PSI class III or less. The beneficial effect of corticosteroids may have been in the more sick patients, since patients in shock and with ARDS benefit from corticosteroids; however, there was no reduction in the time spent in ICU, with both groups having a mean stay of 3 days. Therefore, we may speculate that steroids do have benefit in non-ICU patients. In the South African (SA) context, many patients with CAP would then be necessarily excluded for adjunct corticosteroid use because of high prevalence of HIV <350 cells/μL and tuberculosis. Patients with these two conditions were excluded from the CAP corticosteroid trials.

The Polverino *et al.*[16] prospective observational study, conducted over 10 years, also showed benefits for corticosteroid use in 260 patients, bringing them to stability 1 day earlier than the 2 997 patients not treated with a corticosteroid. However, in sicker patients with pneumonia CURB-65 score 4 or 5, no mortality benefit or faster time to stability was observed.

In contrast to the Blum study,[15] the prospective double blind randomised controlled trial by Snijders,[17] which enrolled 213 patients randomised into groups of 104 patients who received prednisone and 109 who received a placebo, showed no corticosteroid benefit either in mortality or time to stability. The majority of the patients in both groups had CURB-65 scores of between 1 and 3: 90% in the prednisone and 91% in the placebo group. Macrolides were not used as antibiotics in either study group. The time to clinical stability was 4.9 days in each group. The C-reactive protein (CRP) levels had a more rapid decline in the corticosteroid group. Commentary on this study by Meduri *et al.*[18] acknowledged that steroids did not have a role to play in CAP outside the realm of associated severe sepsis.

A study by Tagami *et al.*[19] assessed the use of corticosteroids in severe CAP in patients requiring mechanical ventilation. A total of 6 295 patients from 983 hospitals were divided into those who received catecholamines (n=2 524) and those who did not (n=4 401). In those patients who received catecholamines, two groups of patients were matched using a propensity score with similar physiological variables. The investigators matched 491 patients into two groups, both receiving catecholamines with one group receiving corticosteroids. The mortality rate at 28 days was 25.3% in those receiving additional corticosteroids v. 32.6%. This demonstrated a clear benefit in the use of corticosteroids in patients requiring iontropic support in severe CAP. In the group of 4 401 patients with severe CAP who did not need catecholamine support, patients were matched according to the same propensity scores to give two groups of 943 patients. The mortality in those receiving steroids was 17.7% v. 15.6% (p=0.22), showing no benefit for corticosteroids in ventilated patients who did not receive ionotropic support.

If mechanically ventilated patients with severe CAP who are not in shock do not benefit from the addition of steroids, then the use of steroids in the routine use of CAP treatment in the wards cannot be supported, let alone prescribing steroids with antibiotics for the outpatient management of pneumonia.

Conclusion

Both macrolides and corticosteroids act on inflammatory pathways in infection. It is difficult to target a few pathways in the hope of controlling the body's natural multifaceted response to infection. Studies have struggled to demonstrate a clear benefit for the use of macrolides and corticosteroids to reduce inflammation and thus reduce mortality in CAP. Overwhelming infection causing septic shock appears to be the only clinical indication where corticosteroids have proven to be of benefit in reducing the mortality rate.

The greatest effect clinicians can presently have in reducing the CAP mortality rate is with the widespread use of the pneumococcal vaccine. The adage 'prevention is better than cure' rings true in the realm of CAP, especially as there is increased mortality across all ages in patients with CAP v. control subjects, as much as 10 years after an initial pneumonia.[20]

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