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EDITORIAL

Immunomodulation by antimicrobial drugs

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ABSTRACT

Immunomodulation aims at either enforcement of host defence mechanisms or dampening of the inflammatory response of the host. Thus, immunomodulatory drugs may enhance host defence by either stimulating the inflammatory response or inhibiting the counter-regulatory, anti-inflammatory response. On the other hand, the response of the host may be down-modulated through inhibition of the inflammatory response or induction of counter-regulatory, anti-inflammatory mechanisms. Antimicrobial drugs may have such immunomodulatory effects, but so far these effects have not been exploited clinically.

Many infections are still difficult to treat, despite the availability of potent antimicrobial drugs. Obviously, this is especially the case for infections for which effective antimicrobial treatment is not available because of intrinsic or acquired resistance of the causative micro-organism. We know from animal experiments as well as from clinical studies that antibiotics, even bactericidal ones, may show limited efficacy when host defence mechanisms are defective. This is the reason that scientists have tried to find drugs that are capable of enforcing host defence. As early as in the beginning of the 20th century, George Bernard Shaw alluded to such efforts in his play 'The Doctor's Dilemma' when Sir Ralph Bloomfield Bonington says: 'There is at the bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes. Stimulate the phagocytes'.[1]

On the other side of the coin, the response of the host to infection may be deleterious; proinflammatory cytokines (such as TNF, IL-1, IL-8) and also secretory products of white blood cells (as reactive oxygen metabolites, chloramines, elastase) are able to produce serious tissue damage. Lysis of micro-organisms by host factors (complement, lysosomal enzymes, perforins) as well as by antibiotics may increase these deleterious effects. To try to cope with these effects, drugs that inhibit these effects have been searched for.

In a general sense, immunomodulatory effects of drugs fall into one of the following four categories (or combinations thereof):

1. Stimulation of the inflammatory response (e.g. by increasing the proinflammatory cytokine status or by augmenting phagocyte or T-cell function).
2. Inhibition of the counter-regulatory, anti-inflammatory response (e.g. by inhibiting anti-inflammatory cytokines as IL-10, IL-4 and TGF β).
3. Inhibition of the inflammatory response (e.g. by decreasing the proinflammatory cytokine status, by inhibiting phagocyte or T-cell function or by inducing apoptosis of inflammatory cells).
4. Promotion of the counter-regulatory, anti-inflammatory response (e.g. by increasing anti-inflammatory cytokines as IL-10, IL-4 and TGF β).

It has been known for a number of decades now that antibiotics may also exert effects other than the direct antibacterial ones. The immunomodulatory effects of

antibiotics that have been described fall into the categories mentioned above. However, at this point in time there are a series of problems if we consider the immunomodulatory effects of antibiotics.

- It is hard to delineate under which clinical circumstances we want a certain effect in addition to the antimicrobial action.
- The immunomodulatory effects of antibiotics have mainly been shown *in vitro* or in animal experiments. Many of these studies use rather artificial models, use supratherapeutic concentrations of the drug and are poorly controlled (e.g. for nonspecific effects). Often the antimicrobial effects and the immunomodulatory effects cannot be dissected.
- There is little evidence from the clinical arena that these immunomodulatory actions of antibiotics play a role in terms of outcome. The most convincing in this respect are the anti-inflammatory effects of macrolides and perhaps of tetracyclines.

In this issue of the *Netherlands Journal of Medicine,* the immunomodulatory effects of macrolide antibiotics are critically reviewed by Swords and Rubin,[2] and their paper indicates that it is important for clinicians to be informed and aware of such effects.

REFERENCES

1. Shaw GB. The Doctor's Dilemma. A tragedy. Penguin plays, 1979.
2. Swords, Rubin BK. Macrolide antibiotics, bacterial populations and inflammatory airway disease. Neth J Med 2003;61:241-7.