q8h for various half-lives from 1.5 to 7.3 h, based on data from [9] and [10]. The A/T ratio varies from 0.5 h% to a little more than 2 h% for the AUC/MIC range 25–225 h and is relatively independent of the half-life of the drug.

Thus, the results clearly show that there is no justification for using the AUC/MIC ratio to predict the effect of a drug for which time > MIC is the dynamically linked variable. The principal point and explanation is that a change in MIC will result in a change in both the AUC/MIC ratio and the time > MIC; however, the AUC/MIC ratio changes linearly, whereas the time > MIC changes log-linearly because of the exponential nature of the elimination of most antibiotics. Thus, doubling the MIC will halve the AUC/MIC ratio, but the change in the time > MIC will depend on the half-life of the drug. In general, if there is not too much accumulation of the drug, it will decrease by 1 half-life.

The following additional notes can be made. (1) If the complete dose-effect relationships are used, rather than only those values for AUC/MIC ratios of 25–225 h, then the mismatch between the AUC/MIC ratio and the time > MIC increases dramatically, with A/T ratios ranging from <0.5 to >100 h%. (2) The value of the constant (C) that is presumed to be equal to the A/T ratio is unknown. Depending on the value of this ratio, the “true” effect is either underestimated (i.e., the A/T ratio is <C) or overestimated (i.e., the A/T ratio is >C). Because of the units used for AUC/MIC (i.e., hours) and time > MIC (i.e., percent of time) the presumed value of C is >1 in the range of interest. (3) The relationship between concentration and effect shows a steeper slope for β-lactam antibiotics than for antimicrobials with effects that are dependent on the AUC/MIC ratio; therefore, for β-lactam antibiotics, the change in the A/T ratio does not reflect a similar change in the probability of a positive response over the range of change of the AUC/MIC ratio. Thus, for an AUC/MIC ratio somewhere in the range of 25–225 h, a relatively small change in the time > MIC will result in an increase in effect that is relatively larger than might be expected from the change in the ratio itself.

In conclusion, if the truly dynamically linked index for an antimicrobial is the time > MIC, it makes no sense to use the AUC/MIC ratio to predict the effect of either monotherapy or combination therapy. Either the true effect is underestimated or it is overestimated; in either case, the values of the AUC/MIC ratio will be misleading.

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References

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Clinical Infectious Diseases 2002;35:209–10 © 2002 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2002/3502-0015$15.00

Human Host Defense and Cytokines in Mycobacterial Infectious Diseases: Interleukin-18 Cannot Compensate for Genetic Defects in the Interleukin-12 System

Sir—Cell-mediated immunity plays a critical role in human host defense against intracellular bacteria, including mycobacteria and salmonellae [1, 2]. A key effector cytokine in cell-mediated immunity is the type 1 cytokine IFN-γ, which activates macrophages to promote the killing of intracellular microbes. IFN-γ is produced by T helper 1 lymphocytes and natural killer cells, and its production is controlled by IL-12, a cytokine that is secreted by infected macrophages and dendritic cells.

Recently, several patients were identified who had genetic deficiencies in the type 1 cytokine pathway that controls macrophage activation (as reviewed in [1, 2]). These patients had a strongly impaired capacity to produce or respond to IFN-γ, and, consequently, they were highly susceptible to severe infections caused by poorly pathogenic mycobacteria and Salmonella species [1, 2]. Genetic analyses revealed deleterious mutations in any of 5 different genes in the type 1 cytokine pathway, including mutations in IL12B (which encodes the p40 subunit of IL-12), IL12RBI (which encodes the β1 subunit of the IL-12 receptor [IL-12Rβ1]), IFNGRI and IFNGR2 (which encode the IFN-γ receptor chains associated with ligand binding [IFNγR1] and signaling...
[IFNγR2], respectively), and STAT1 (which encodes the signal transduction molecule Stat-1 associated with IFNγR1). Of interest, the severity of the clinical and histopathological phenotypes of the patients differed markedly, probably as a result of the action of compensatory immunological mechanisms, although none have been identified [1, 2].

IL-18 recently has been described as a second major cytokine (in addition to IL-12) that promotes IFN-γ production and type 1 cell–mediated immunity [3, 4]. In gene knockout mice, the effect of the IL-18/IL-18 receptor (IL-18R) pathway was reported to be codominant with the IL-12/IL-12 receptor (IL-12R) pathway [4]; however, in humans, the precise biological role of IL-18 remains incompletely defined independent of the IL-12 system. To investigate whether IL-18 can substitute for IL-12 in the induction of cellular immunity and IFN-γ production in humans and whether IL-18 thus could provide novel opportunities for immunotherapy for immunodeficient patients, we investigated the role of the IL-18/IL-18R pathway in the absence of a functional IL-12/IL-12R system.

Our study involved a unique group of genetically IL-12Rβ1–deficient individuals who we recently identified [5, 6]. All 9 patients (3 adults and 6 children) had severe infections caused by either poorly pathogenic mycobacteria (Mycobacterium avium or Mycobacterium bovis BCG) or Salmonella species, had deficient IFN-γ production, lacked cell-surface expression of IL-12Rβ1, failed to respond to exogenously added IL-12, and had deleterious recessive mutations in IL12RBI [5]. In contrast, we found no such defects in healthy control subjects or the parents of our patients [5, 6]. All adult patients, in addition to the parents of patients who were children, provided written informed consent to participate in the study. The protocol was approved by the medical ethical board of the Leiden University Medical Center.

The results of our study indicated that IL-18 production, expression of the IL-18Rα chain, and IL-18R signaling are not enhanced in patients with IL-12Rβ1 deficiency, compared with control subjects (figure 1). The levels of IL-18 produced by the cells of IL-12Rβ1–deficient patients were comparable to, or slightly lower than, those of patients with complete or partial IFNγR1 deficiency (not shown) or those of healthy control subjects. Blocking the bioactivity of IL-18 or IL-12 by neutralizing monoclonal antibodies confirmed that IL-18 had less effect on IFN-γ production than did IL-12 (data not shown). Stimulation of patients’ cells with IL-18 (in the absence or presence of IL-12) did not trigger significant levels of IFN-γ production, compared with IL-18 stimulation of cells of IL-12Rβ1–competent individuals (figure 1).

These results indicate that, in humans, (1) IL-18 alone does not act as a major pathway of IFN-γ production, independent of the IL-12/IL-12R system [5], and (2) the IL-18/IL-18R system cannot substitute for the IL-12/IL-12R system. Thus, in cases of intracellular infectious disease in humans, the effect of the IL-12/IL-12R pathway clearly seems dominant and primary, compared with that of the IL-18 system. This finding seems to contrast with observations in IL-18 gene knockout animals [4]. On the basis of the aforementioned findings, the immunotherapeutic potential of IL-18 in infectious diseases in humans with IL-12R deficiency may be limited, given the relatively low increase in IFN-γ production in response to IL-18 in the absence or presence of IL-12. Moreover, our results may explain why no genetic defects have yet been found in IL-18 or IL-18R (data not shown), despite

Figure 1. IL-12 responsiveness in patients with genetic deficiency of the β1 subunit of the IL-12 receptor (IL-12Rβ1) and in control subjects. The IL-18/IL-18 receptor (IL-18R) system does not compensate for IL-12 receptor (IL-12R) deficiency in genetically IL-12Rβ1–deficient patients. Peripheral blood mononuclear cells (PBMCs) were isolated using standard Ficoll-Hypaque density gradient centrifugation. Cells were incubated (8 × 10⁵ cells/well) and were stimulated with control medium or lipopolysaccharide (100 ng/mL). IL-18 production in the supernatant was measured 6 h later by use of an ELISA described elsewhere [6]. Expression of IL-18R and IL-12R was determined on phytohemagglutinin-activated PBMC blasts, as described elsewhere [5, 6]. Responsiveness to IL-12 or IL-18 was determined by stimulation of PBMCs by mitogenic antibodies in the presence or absence of recombinant IL-12 (2.5–10 ng/mL; R&D Systems), recombinant IL-18 (50–100 ng/mL; provided by M.K.), or a combination of both [5, 6]. IFN-γ levels in the supernatant were determined by ELISA, as described elsewhere [5]. SI, stimulation index (i.e., IFN-γ production in the presence of the indicated stimuli divided by IFN-γ production in the absence of the indicated stimuli).
several genetic defects in IL-12/IL-12R, IFN-γR, and Stat-1 having been found in patients who had unusually severe infectious diseases caused by poorly virulent mycobacteria and salmonellae [1, 2].

**Acknowledgments**

The support of The Netherlands Leprosy Relief Foundation (Amsterdam), The Netherlands Organisation for Scientific Research (The Hague), and the Commission of the European Communities (Brussels, Belgium) is gratefully acknowledged.

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