



When good drugs turn weirdly bad

More and more patients are receiving highly specific anti-inflammatory and immunosuppressive medications. As Drs. Derek Tang and Lawrence Ward (page 472) emphasize in this issue of the *Journal*, these drugs have side effects, some predictable and some surprising. Because they blunt the immune response (which is why we give them), our concern about opportunistic infection is naturally high, but we must also recognize some seemingly paradoxical reactions.

Many of the adverse effects of the small-molecule drugs such as azathioprine (Imuran) and methotrexate are those expected from chemical toxicity or inhibition of proliferation, eg, aminotransferase elevation, leukopenia, and alopecia. Mycophenolate mofetil (CellCept) uniquely can cause profound anemia, cyclophosphamide (Cytoxan) elicits cystitis, and many of these drugs trigger virus-associated malignancies. In perhaps 8% of patients, azathioprine causes a systemic hypersensitivity reaction with high fevers, variable rash, leukocytosis, and elevated aminotransferase levels shortly after it is started. Yet we are often slow to recognize this syndrome, as we tend to search for an infection and forget that even immunosuppressive drugs can cause systemic allergic-type reactions. A similar syndrome following initiation of phenytoin (Dilantin) would be recognized far more rapidly.

But the biologic agents, which target specific components of the immune system, resulting in focal immunosuppression and a disturbance in the homeostatic balance of the immune system, elicit some of the more challenging and sometimes paradoxical side effects. Interferon alfa, which has antiviral effects, is also used as an immunomodulator to treat Behçet disease and as part of regimens that treat specific malignancies. Perhaps because it up-regulates the expression of major histocompatibility complex class II molecules on antigen-presenting cells, interferon therapy also triggers several organ-specific autoimmune syndromes, including autoimmune thrombocytopenia, hypothyroidism, hemolytic anemia, hepatitis, and psoriasis.

Even more challenging to understand and sometimes to treat are the inflammatory effects of anti-tumor necrosis factor agents. Drugs of this class can evoke a demyelinating syndrome similar to multiple sclerosis. Further, even though they are used to treat psoriasis, they can also provoke a psoriasiform, often palmar and pustular, reaction.

So as we continue to adopt targeted immunologic therapies and revel in their efficacy, we need to remain humbled by what we don't yet fully understand about the complexity of what the 19th century physiologist Claude Bernard termed the *milieu intérieur* (homeostasis) and keep in mind that even the most specific of drugs can have untoward biologic effects by weirdly disrupting our finely balanced immune system.

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