Editorial

Infections, Drugs, and Rheumatoid Arthritis. What Have We Learned?

According to French writer Sebastian-Roch Nicolas de Chamfort, in his *Maximes et Pensées*, "Philosophy, like medicine, has plenty of drugs, few good remedies, and hardly any specific cures." One can easily substitute rheumatoid arthritis (RA) for philosophy and occasionally question whether our drugs used for RA are "good remedies."

It is and has been well known that the longterm morbidity and mortality are higher in RA versus the general population. Reasons for increased morbidity and mortality include, among others, increased risk of infections, cardiovascular diseases, pulmonary complications, and neoplasms including non-Hodgkin's lymphoma. However, there is still no clear indication why this is so, or what component of this increased risk is due to the disease itself, to comorbid factors associated with ill health in general (diabetes, cancer, heart and renal disease), or even to the drugs we use to treat the disease. While we assume our new therapies have decreased morbidity and mortality, there are studies that show this may not be true[1].

Recently, Gonzalez, *et al* reported that mortality in patients with RA was similar across 2 different treatment eras, the latter being the period encompassing use of biologic therapies (albeit perhaps without a long enough longitudinal sample[2]).

Indeed, the level of concern has heightened as we use more potent molecules that inhibit the immune system. Since 1998 there has been an explosion in the use of drugs to treat RA, with the introduction of leflunomide, infliximab, etanercept, anakinra, adalimumab, abatacept, and rituximab. We would like to believe that our treatments will lead to fewer complications, prolonged disease-free intervals, as well as prolonged lifespans. However, the more one looks, the more the veil lifts, revealing reasons for increased morbidity regarding, in particular, infection and cardiovascular diseases.

But there is still a relative lack of clarity defining the reasons for infection in RA. Is an observed increased risk due to the disease or its treatment; and if the latter, which treatment protects our patients with RA and which treatment makes them more vulnerable to infection?

Virtually all RA studies looking at the causes of mortality have shown increased risk of infection. In some studies the excess death rate from infection was 5.5-fold for RA patients compared with controls[3]. However, a more germane question in the era of biologics is: What percentage of patients with RA are hospitalized with infections? This question, which more cogently addresses the ambulatory life experience of the RA patient currently being treated, has been reviewed many times. Doran, *et al* found a significantly increased risk of infection in patients with RA[4], but other studies have not shown the same outcomes[5,6]. This may be due to differences in patient populations (not controlled for severity) and in control groups (not controlled for age, sex, comorbidities). However, there is a belief among practicing rheumatologists that RA patients not only have increased risk of infection, but also increased severity when infected, particularly when taking disease modifying antirheumatic drugs, and especially biologic therapies. However, it is only recently that these discrepancies are being teased out and dissected as to why. Is it disease severity? Is it drug therapy? Is it one particular drug?

In this issue of *The Journal* Smitten, *et al* describe their retrospective study from 1999 to 2006 including 24,530 RA patients and 500,000 controls, in which individuals with RA were observed to have an increased risk of being hospitalized for an infection[7]. In a nested case-control analysis, oral corticosteroid use was associated with a dose related increase, and the biologic therapies were associated with only a slightly increased risk. Patients treated with hydroxychloroquine and methotrexate had a decreased risk of hospitalized infections.

The advantages of this study are the large number of patients in the RA group and the number of patients who had received at least one biologic (24%). When one further

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dissects the RA group, those with infections, not surprisingly, were more likely to be older, diabetic, have chronic lung diseases, and to have been previously hospitalized; however, the use of biologics only slightly increased the risk of hospitalized infection (relative risk 1.21; 95% CI 1.02–1.43). Interestingly, methotrexate use and hydroxychloroquine use were associated with decreased risk, and other non-biologics had no association.

What is surprising is that the risk of infection was most associated with increasing doses of steroids, but even at doses ≤ 5 mg/day the risk of hospitalization for infections increased (RR = 1.32; 95% CI 1.06–1.63). This risk is slightly higher than the risk of infection with biologic therapies!

What is the practicing clinician to make of this information? Is it a surprise that patients with RA have an increased risk of hospitalized infections, especially in the post-gold treatment era? In a recent publication, Schneeweiss, *et al* reported that in a large cohort of patients with RA there was no increase in serious bacterial infections among users of anti-TNF therapy compared with users of methotrexate[8]. However, a dose-dependent increase in infections was noted in patients with RA who used corticosteroids, with those using < 5 mg prednisone having a RR of 1.34, peaking at RR of 5.48 for those using > 20 mg prednisone daily.

The efficacy of corticosteroids in RA is unquestioned. They are often used for comfort, but a significant body of literature confirms they add disease-altering properties, particularly when used as part of a multiple drug regimen[9,10]. However, with the advent of newer therapies, the use of corticosteroids has, perhaps, become too generally accepted. As entry criteria for virtually all drug studies the use of corticosteroids is allowed as long as the dose does not exceed a certain threshold. Studies clearly show that there is an increased risk of weight gain, skin frailty, and osteoporosis when used as a treatment for RA, and there are now compelling signals that perhaps we should reconsider the dose and duration of corticosteroid therapy in RA. Smitten's study confirms a finding of many others: a common thread in the increased risk of infections and hospitalizations is the use of prednisone. Strikingly, this increase may start at doses of 5 mg/day or less[7].

That RA carries a risk of increased infections is accepted; similarly, it is no surprise that infections may be associated with anti-tumor necrosis factor therapies (at least regarding severity, if not frequency). What is concerning are the accumulating data associating risk of infection to even low doses of steroids. Rheumatologists may be at a time, with much more potent therapies available and after patients achieve a stable disease state, to become more committed to getting our patients off steroids altogether, or at least continue to strive for the lowest possible dose acceptable for disease control.

Perhaps de Chamfort was correct. Our remedies may not be good enough (although they are so much better!), and there are certainly no "cures," but we have progressed so far in such a short time that we must now take stock. It may be time to look at our accepted therapies that have been assumed to be "benign." Shouldn't we be even more vigilant to use the correct remedy at the correct dose for the correct time?

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