Corticosteroids for Recurrent Pericarditis
On the Road to Evidence-Based Medicine

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e have known for decades that acute pericarditis may recur after apparent cure.1 In spite of recent advances, recurrence, after an initial attack of acute pericarditis, remains a challenge for many reasons. For example, the exact rate of recurrence is not known because many, if not most, cases go unreported, especially those that have a benign course and respond quickly and completely to a nonsteroidal antiinflammatory agent (NSAID), such as ibuprofen, indomethacin, or aspirin. The evidence that, in most cases, recurrence is an autoimmune response to the initial pericardial insult is compelling,2 but we still lack an inexpensive, harmless, readily available test that reliably separates autoimmune reoccurrence from recurrence of another cause, notably infection. The distinction is important, because corticosteroid therapy is required for some of the immunogenic cases of recurrent pericarditis but is contraindicated in cases caused by infection. Reports from tertiary referral centers include a high proportion of patients who did not improve after treatment with prednisone, or had serious steroid-induced side effects.

High-dose corticosteroid became the accepted standard treatment for recurrent acute pericarditis long before the concept of evidence-based medicine and guidelines was introduced and therefore was based on the anecdotal experience of medical and surgical cardiologists whose subspecialty was pericardial disease. One of the most influential of these was the report by Fowler.2

Imazio et al3 therefore, whose report is published in the current issue of Circulation, searched the literature for clinical trials of steroidal treatment for recurrent pericarditis but found only the report by Marcolongo et al,4 who reported that high-dose prednisone given for 1 month and followed by a slow dose reduction and the addition of large doses of aspirin for 5 months, then by low-dose aspirin for another 3 months, was highly effective therapy for recurrent acute pericarditis, whereas lower doses were ineffective. As Imazio et al state, however, this was a small single-center retrospective study of only 12 patients. Thus, although it appeared to support past and current practice of using high-dose prednisone, it fell far short of making high-dose steroids an evidence-based treatment regimen for recurrent pericarditis. Furthermore, 8 months of aspirin included in Marcolongo’s protocol make it impossible to state with certainty that the excellent results in 11 of the patients receiving at least 1 mg/Kg per day can be attributed to the dose of prednisone.

Most physicians treat recurrence of pericarditis with an NSAID, but when it is not promptly aborted or recurs again, switch to high-dose prednisone or another corticosteroid. The guidelines for treating pericardial disease issued by the European Society of Cardiology in 2004 recommended 1 to 1.5 mg/Kg per day.5 In spite of extensive patient and continuing medical education, others still begin treatment with a corticosteroid. Current recommendations are to start treatment with an NSAID plus colchicine and avoid corticosteroid drugs whenever possible. Only when a thorough and determined effort to treat with an NSAID has proven to be clearly unsuccessful, is not tolerated, or is contraindicated is high-dose prednisone, usually 1 mg/Kg per day, advised.6

When Imazio et al searched the literature for clinical trials of corticosteroid treatment of recurrent pericarditis, they found only the single small study by Marcolongo et al that supported using prednisone, at least initially, at high dose, and knowing that rheumatoid arthritis and similar collagen-vascular diseases, much more common autoimmune-mediated diseases, are well managed with 0.1 to 0.5 mg/Kg per day of prednisone, they conducted their nonrandomized observational study reported in this issue of Circulation, of high-versus low-dose prednisone to determine whether or not high-dose prednisone is really required for recurrent pericarditis.3

The study was performed at 2 Italian tertiary referral hospitals, one in Torino, the other in Milano. At the Torino center, prednisone, when clinically indicated, was administered at 1 mg/Kg per day for 4 weeks and gradually tapered, as in their prestudy clinical protocol, whereas at the Milano hospital, the 4-week loading dose was 0.1 to 0.5 mg/Kg per day, also the same as it had been in their prestudy clinical protocol. Aside from the different prednisone doses, the study protocol was identical at the 2 hospitals. A total of 100 patients, who had been treated during a period of ~5.5 years, constituted the study population. Approximately half of the patients received the higher dose. The patients at the 2
institutions were well matched for all relevant variables at baseline.

The results go a long way to establishing that the lower dose may be more appropriate than the higher one. Severe side effects were found in 23.5% of the patients who received the higher dose versus only 2% in those who received the lower dose \( (P=0.002) \). That serious side effects were more common with the higher dose is hardly surprising, but the magnitude of the difference is greater than may have been anticipated. The recurrence rate in patients receiving the higher dose was 64.7% versus 32.6% in the lower-dose group \( (P=0.002) \). Thus, paradoxically, the outcome of using the higher dose was to double the recurrence rate. This result is in striking contrast to that of Marcolongo et al\(^4\) and would not have been predicted by most clinicians. Corticosteroid, usually commenced at a high dose, dramatically and quickly abolishes the symptoms and signs of acute pericarditis and its recurrences. Thus, the same drug that can end an acute recurrence can promote further recurrences. The mechanism responsible for this paradox has not been established. Corticosteroid therapy also, however, attenuates the benefits of adding colchicine to the therapeutic regimen.\(^7\)

It is predictable that the use of lower-dose prednisone will be extended to other pericardial injuries, including the pericardiotomy syndrome and delayed pericardial pain after acute myocardial infarction (Dressler syndrome).

The duration of corticosteroid treatment is as important as the loading dose. Anxiety about the potential for severe side effects of prednisone appears to be the reason that the loading dose is frequently lowered after only a few days instead of the recommended 1 month, and the taper has often been too rapid, leading to an unsuccessful outcome in spite of a high loading dose. For examples of satisfactory tapering schedules, see Figure 1 in Imazio et al.\(^3\) Recurrent pain, indistinguishable from that of pericarditis but without clinical or laboratory evidence of disease in patients with previous idiopathic or viral pericarditis, and indeed of inflammation, is a fairly common phenomenon,\(^8\) but its pathogenesis is not understood. Suffice it to say here that it should be treated with an analgesic, not immunosuppressive drugs. In my experience, most of these patients have received prednisone, often on several occasions. Imazio has pioneered clinical trials of colchicine for acute and recurrent pericarditis, moving this topic in the direction of evidence-based treatment.\(^9\) Patients concerned about prednisone toxicity or who remain symptomatic in spite of pharmacological treatment often inquire about the alternative of pericardiectomy. Basing their opinion on anecdotal data, physicians usually advise that this procedure should be considered a last resort. Pericardiectomy banishes acute recurrent pericarditis in an unknown proportion of cases and, to make matters worse, no known way exists to predict the result of the operation. Furthermore, some of the patients develop pleurisy, with or without effusion, postoperatively. No clinical trials comparing the 2 treatments have been published but would be welcome if they were. The best surgical results are those of Tuna et al.\(^10\) These authors stress the importance of removing as much pericardial tissue as possible. Patients should be referred to surgeons with a special interest in pericardial surgery.

Physicians should be reluctant to use a corticosteroid for recurrent pericarditis but strive to treat the patients with an NSAID. In this way, significant complications can be avoided. When it is clear that steroid use is inevitable, the duration of treatment and the schedule for tapering should be the ones recommended by Imazio et al.\(^3\) More data will be needed before the lower loading dose can be recommended, but with the data we do have, it would be a reasonable alternative.

## Disclosures

None.

## References
