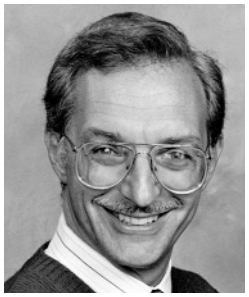
Editorial



Window of Opportunity

When does it start?

Although the pathogenesis of rheumatoid arthritis (RA) is not fully understood, it is felt to involve the interaction of antigen-presenting cells with an antigen, with continued interactions between the antigen-presenting cell, T cells, synoviocytes, and B cells. Associated with these interactions is the release of numerous cytokines and enzymes, resulting in inflammation and damage[1]. These events start long before any clinical findings. For example, Nielen, *et al* found that patients with arthritis have rheumatoid factor in their blood for a median of 4.5 years before their first clinical symptom[2]. It seems very likely, then, that there is a "ramping up" of autoimmune activity and a certain autoimmune load of cells will have built up before clinical symptoms arise. Boers, in his discussion of a window of opportunity, opined that treating early and aggressively would allow one to prevent the disease from becoming established[3]. In this construct, one might wish treatment when RA first begins. In an analogy to oncology, one could consider this "de-bulking" the totality of the autoimmune system and the earlier this is done, the more effective it will be. In this analogy, our present-day medications would not be as effective given later as given early; and this time period of greatest effectiveness is the window of opportunity.

And when considering the opening of a window of opportunity, one must also consider the concept of *closing* such a window. First, do the data demonstrate that treating at an early point after RA begins is more effective than treating later?

Anderson, *et al* did a metaanalysis of 14 randomized, controlled trials involving methotrexate (12 trials), an induction trial using combination therapy in early RA, and a placebo controlled trial of a device[4]. Response to treatment was strongly affected by disease duration: patients with disease duration of less than 1 year had a 53% response rate, those whose disease duration was 1–2 years had a 43% response rate, those with disease duration of 2–5 years responded 44% of the time, while those whose disease duration was 5–10 years responded 38% of the time. Tsakonas, *et al* tested early versus delayed treatment with hydroxychloroquine (HCQ) in a randomized trial of 119 patients with early RA[5]. Patients received HCQ (early treatment) or placebo (delayed treatment) for 9 months; then all patients were treated and followed for an additional 3 years. The delayed treatment group had more pain and disability for the whole 3-year followup period, although global well being was the same by 2 years of followup. Borg, *et al*, in a double-blind, randomized study, treated patients with < 2 years' disease with auranofin or placebo and followed patients for 24 months. An average 8 month delay in starting auranofin was still discernible as less joint swelling and less radiographic progression at 24 months[6]. A nonrandomized trial by Lard, *et al* followed 206 RA patients for 2 years, treating an early treatment group of 97 RA patients with chloroquine (CQ) or sulfasalazine (SSZ) versus delayed treatment (analgesics followed by CQ or SSZ if needed) in 109 patients[7]. The median time to starting CQ or SSZ was delayed by about 15 weeks in the delayed treatment group. After 2 years, the area under the curve of the disease activity score (DAS) was less in the early treatment group (64 vs 73 DAS units, $p = 0.002$) and there was less radiographic damage as well (3.5 vs 10 Sharp units, $p < 0.05$). These results are mitigated by the nonrandomized, open study design but are supportive of the general concept that early treatment is more effective than delayed therapy. Kanevskaya and Chichassova examined the effect of beginning disease modifying antirheumatic drug (DMARD) therapy within 6 months (N = 62), at 6–11 months (N = 72) or 12–36 months after RA diagnosis (N = 106)[8]. Sustained remission was observed more frequently during up to 15 years of followup in those whose treatment began early — 59% in those treated within 6 months versus 15% whose therapy began between 12 and 36 months ($p < 0.001$). Radiographic change, too, was less in the early treatment group throughout the 15-year followup ($p < 0.01$ for erosions). Like the study of Lard, this

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study suffered from its open nonrandomized study design, introducing the likelihood of selection and treatment bias, but it again supports the concept that early DMARD therapy is more effective.

Not all studies were quite as positive, however. Van der Heijde, *et al* performed an open, randomized trial of 238 RA patients, comparing immediate versus delayed treatment with DMARD[9]. The delayed treatment group started therapy with nonsteroidal antiinflammatory drugs (NSAID); DMARD were started when clinically indicated. The early treatment groups started HCQ, intramuscular gold, or MTX. Although average time to starting DMARD was not available, 71% of the NSAID-only group were still on that therapy after one year; thus 71% of this group delayed DMARD for one year. Mean disease duration and other baseline characteristics were comparable. Statistical differences ($p < 0.05$ (?)) in disability (0.3 units of a maximum 3.0), joint score (39 units of a maximum 534), and erythrocyte sedimentation rate (11 mm/h, range 1–140) were found at 6 and 12 months but that difference had disappeared by 5 years[10]. Here, the difference at 12 but not 60 months might have been due to lack of continued aggressive therapy for the whole study duration; at least that is the postulate of the author of this 5 year followup report[10].

In this issue of *The Journal*, Amjadi-Begvand and colleagues point out that patient memory is often faulty — higher disease activity tended to telescope time and the longer the time from first report, the more inaccurate the memory[11]. Since 3 years of disease is sometimes used as the "cutpoint" for early disease, one could look at the date at 39 months in the Amjadi-Begvand article. There was an average 10.2-month overestimate of disease duration by 18% of patients at 38 months and a 6.5-month underestimation by another 30% of patients at the same timepoint (nearly 50% inaccurate memory). Longer disease duration, lower disease activity, and increased pain were associated with less accuracy.

What does this apparent inaccuracy of memory mean to the concept of the window of opportunity? Why, by the way, is this definition of disease start so important anyway? As to the latter, a definition of the start of disease may be important if the pathogenesis of RA undergoes change over time. For example, it is now thought that T cells are more important early in disease pathogenesis, but that macrophages and synoviocytes become more central to disease pathogenesis later[12]. In that case, defining disease onset would help define the best therapy for a patient. T cell-directed therapy might be best earlier in disease course, while aiming therapy more at macrophages and synoviocytes later on would be best. It would be silly to assume that only one cell type is active at any point in the disease; however, the use of therapy that is directed more at one cell type than at another may well result in more effective disease control with less toxicity than the use of shotgun approaches throughout the disease course. These more targeted approaches, of course, are only now becoming possible as our armamentarium becomes more specific and understood.

It is in this context that the window of opportunity is set, although the clinical definition of the window of opportunity may encompass several phases of disease defined by the previous discussion. Only with a uniform definition of disease duration can we understand and design studies that will be generalizable to our patients in the clinic. Also, it is within this early period (the window of opportunity) that understanding the dual concepts of de-bulking and dynamic pathogenesis will help us treat our patients most effectively.

Given the interesting and challenging data from Amjadi-Begvand, *et al*[11], it would be worthwhile to consider some possible ways forward. One approach could be to define disease start (and window of opportunity) from the date of diagnosis. This is a point that can be more easily defined because one can look into patient charts for the specific data. However, this seems unlikely to be better than the present approach because it builds in difficulties relating to variable access to care and finding the medical chart in patients who move from one doctor or health management organization to another.

Another approach is to define the diagnosis based on laboratory data. This is certainly objective — for example, if one defines disease as rheumatoid factor/anti-cyclic citrullinated peptide positivity or by a certain magnetic resonance or ultrasound imaging. This definition is confounded by the same issues as above (access to care to do the test, problems with finding the medical record), plus the lack of agreement about which laboratory or objective measure will be used.

Or one could continue to use the present approach using patient memory as our standard — while realizing that this is inaccurate — and understanding its limitations. Perhaps we can at least lend uniformity to this definition by seeking data from the medical chart in all cases, as well as patient memory, using the earliest point as the time of disease start. Clearly, some further thought, agreement, and written definition of this important point would be useful to the rheumatologic community. We could use, for example, the help of organizations such as OMERACT or the American College of Rheumatology.

To conclude, let us not forget the second concept: is *closing* the window of opportunity of any importance? And how could one define the closing of such a time period? It is possible that there is a time period during which it is more likely that remission of RA can be induced, as implied by Kanevskaya and Chichassova, but that this likelihood decreases, to a very large degree, beyond some as-yet undefined point (closing the window). If one uses remission as the desired endpoint, one could try to define closing the window of opportunity as the point at which the probability of remission becomes less than a given value (for example, 5%).

Obviously, patients are able to respond to treatment to some degree throughout the course of their disease, so that the term closing the window of opportunity is not meant to be

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absolute. Nevertheless, if one could define a time period beyond which it is very unlikely that remission can be induced, one might be able to avoid the toxicity of overly aggressive therapy when there is a very low probability of achieving the desired response. The idea that the window of opportunity may close, or nearly close, is one that deserves further discussion.

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REFERENCES

1. Harris ED Jr, Budd RC, Firestein GS, et al. Kelly's textbook of rheumatology. Philadelphia: W.B. Saunders Co.; 2001.
2. Nielen MM, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004;50:380-6.
3. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum 2003;48:1771-4.
4. Anderson JJ, Wells G, Verhoeven AC, et al. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000;43:22-9.
5. Tsakonas E, Fitzgerald AA, Fitzcharles MA, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the Hydroxychloroquine in Early Rheumatoid Arthritis (HERA) study. J Rheumatol 2000;27:623-9.
6. Borg G, Allander E, Lund B, et al. Auranofin improves outcome in early rheumatoid arthritis. Results from a 2-year, double blind placebo controlled study. J Rheumatol 1988;15:1747-54.
7. Lard LR, Visser H, Speyer I, et al. Early versus delayed treatment in patients with recent onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446-51.
8. Kanevskaya MZ, Chichassova NV. Treatment of early RA: influence on activity and x-ray progression in a long-term, prospective study [abstract]. EULAR 2003, Lisbon, Portugal. Internet. [cited June 16, 2004]. Available from www://http.eular.org
9. Van der Heijde A, Jacobs JWG, van der Veen MJ, et al. The effectiveness of early treatment with "second line" anti-rheumatic drugs, a randomized, controlled trial. Ann Intern Med 1996;124:699-707.
10. Verstappen S, Jacobs J, Bijlsma J, et al. Five-year followup of rheumatoid arthritis patients after early treatment with disease-modifying anti-rheumatic drugs versus treatment according to the pyramid approach in the first year. Arthritis Rheum 2003; 48:1797-807.
11. Amjadi-Begvand S, Khanna D, Park GS, Bulpitt KJ, Wong WK, Paulus HE. Dating the "window of therapeutic opportunity" in early rheumatoid arthritis: accuracy of patient recall of arthritis symptom onset. J Rheumatol 2004;31:1686-92.
12. Firestein G. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356-61.

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