Editorial

Speculations on Why Early Treatment of Rheumatoid Arthritis Is Uniquely Effective

Is it a greater remission rate, or are we preventing onset of rheumatoid arthritis?

Dating back to 1909 there have been multiple reports that early treatment of "rheumatoid arthritis" (RA) is uniquely effective[1,4]. Recent reports suggest that early treatment induces a high remission rate and slows the progression of structural damage during and after the initial treatment phase. In 1999, Finnish investigators reported that 195 patients randomized to 2 treatments, sulfasalazine (SSZ) alone or a combination of SSZ, methotrexate (MTX), hydroxychloroquine (HCQ), and low-dose prednisolone, had remission rates of 35% and 42%, respectively, when treated within the first 4 months after disease onset[5]. Those who received monotherapy between 4 and 24 months after onset had a remission rate of only 11%, while those treated with the combination continued to have a remission rate of 42%. Progression of structural damage was significantly slower in the combination group during the 2 years of treatment on the protocol and persisted for 3 years longer[6]. Was the remission rate observed in the FIN-RACo study uniquely high? Table 1 lists data on American College of Rheumatology (ACR) improvement and remission rates for comparison[7-12]. Remission rates were reported for only 2 studies; however, accepting ACR70 and ACR90 as representing the highest possible remission rate, these studies are strikingly different from the FIN-RACo[8,9]. Eberhardt and colleagues observed remissions of 6 months or longer in 20% of 183 patients seen in the first 6 months of disease and treated without biologics[8]. The Hetland report on patients in the first 6 months of disease is further evidence that early treatment induces a high remission rate[9]. In other reports ACR70 rates were not above 26%.

Smolen and his colleagues have pointed out the slightly greater baseline values for several clinical features of disease activity and radiographic scores in the monotherapy group and suggested that these differences in prognostic features may explain the difference in results for those seen between 4 and 24 months, but are these very small differences sufficient explanation[13]? Similar remission rates in those treated in the first 4 months are in stark contrast to the remission rates in those patients treated later. Is there a hypothesis that would explain this result?

Are we unknowingly preventing RA?

If we acknowledge that the diagnosis of early RA is uncertain and that such a cohort almost certainly is a mixed population, I think there is such a hypothesis. How certain is the diagnosis of RA in patients seen soon after onset of joint pain and swelling who have no structural damage? At what point can the investigator decide with confidence that a patient has RA rather than undifferentiated arthritis? If we assume that patients seen in the first few months of articular symptoms and signs have a mixture of RA and undifferentiated synovitis, we can construct a logical explanation for their high remission rate when treated early. Most patients with undifferentiated synovitis have spontaneous remission after a few weeks or months[14]. It is logical to assume that the proportion of patients mistakenly recruited as having early RA who instead have undifferentiated synovitis diminishes the longer symptoms persist, with a concomitant increase in the number of patients who have RA. This explains the high remission rate regardless of treatment in the FIN-RACo patients seen very early after onset, and the fall in remission rate of those taking monotherapy first seen later, a remission rate that more closely resembles the usually observed rate. The continued high remission rate in the combination arm among those first seen after 4 months of symptoms is unique.

How to explain the unexpectedly high remission rate of those treated with drug combination whose first visit was delayed past 4 months?

If it is agreed that there are 3 types of patients in the Finnish cohort, then 5% to 11% had undifferentiated synovitis that went into remission — presumably their disease would have remitted even without treatment; 58% had established RA when first seen or were seen too late to stop the process and had progression of disease despite treatment; and 31% had what I will call "nascent RA." By postulating that combination therapy, but not monotherapy, prevented development of RA in the nascent RA group, the greater remission rate is explained.

Supporting studies

Several other trials support the unexpectedly strong effect

Table 1. Remission in selected RA trials[a].

Investigator	Disease Duration, yrs (average months)	No.	Treatment	ACR70, %	ACR90, %	ACR-Rem, %
O'Dell[7]	6.9	171	MTX + HCQ[b]	16		
			MTX + SSZ	18		
			MTX + SSZ + HCQ	26		
Eberhardt[8]	< 2 (11.1)	183	DMARD[c], steroids allowed			20
Hetland[9]	< 0.5	80	CSA + MTX, IAS[d]			35
		80	MTX + IAS			28
Bathon[10]	< 3	217	MTX	22		
		208	ETA 10 mg/wk	16		
		207	ETA 25 mg/wk	25		
St. Clair[11]	< 3	252	MTX + PBO		6.6	
		359	MTX + INF 3 mg/k		10	
		363	MTX + INF 6 mg/k		16.9	
Breedveld[12]	< 3	257	MTX + PBO		13	
		274	ADA + PBO		9	
		268	ADA + MTX		27	

[a] Table includes the data from an O'Dell combination trial and trials that admitted patients with disease duration < 3 years and data on remission rates or ACR response criteria rates. [b] 58 patients received methotrexate (MTX) and hydroxychloroquine (HCQ); 55 received MTX and sulfasalazine (SSZ); and 58 received MTX, HCQ, and SSZ. [c] 114 patients received 1 or more disease modifying antirheumatic drugs (DMARD) including MTX (6), SSZ (21), gold (25), penicillamine (51), chloroquine (68). 29 patients received steroids, dose not stated. [d] Intraarticular betamethasone (IAS) was injected in all active joints in each group at baseline and every 2 weeks for 2 months, then every 4 weeks. PBO: placebo; INF: infliximab; ETA: etanercept; ADA: adalimumab; CSA: cyclosporin A.

of early treatment. The COBRA trial, like the FIN-RACo, compared SSZ monotherapy with combination therapy in patients with RA of less than 2 years' duration but used a slightly different mix of drugs: SSZ, MTX, and high-dose, rapidly tapered prednisolone[15,16]. The radiographic progression rate in the combination therapy arm was about 60% of that in the monotherapy arm after one year of protocol therapy, and this difference in radiographic progression lasted through 4 years, during which both treatment arms received similar medications. That study also has been criticized because the baseline radiographic score in the combination treatment arm was only 60% of that seen in the monotherapy arm. However, a radiographic score and a radiographic progression rate are different things. Because the variance is much greater in the raw scores than in the change scores, the baseline radiographic scores were not significantly different and do not predict faster progression of damage.

The BeSt trial resolves the doubt about cohort similarities in the FIN-RACo and the COBRA trials. The BeSt investigators used the same study design employed in the COBRA trial for one of 4 treatment arms[17]. The MTX, SSZ, and prednisolone arm reproduced the COBRA and FIN-RACo radiographic results, and the baseline radiographic scores were very similar in all treatment arms.

Which drug in the combination is responsible, or are all drugs required?

All the therapeutic agents used in these trials have immunosuppressive effects, and several have antibacterial properties. Combinations of these agents may have additive or synergistic immunosuppressive effects that could be responsible for the observations in these early RA trials. Smolen, *et al* emphasized the potential of glucocorticoids, and it is noteworthy that steroids were used in the FIN-RACo, COBRA, and BeSt trials, albeit at a much lower dose in FIN-RACo[13]. O'Dell, *et al* found that a combination of MTX, SSZ, and HCQ was superior to MTX plus SSZ and marginally superior to MTX plus HCQ[7]. More studies are needed to pinpoint which agent or combination is required to induce the observed prolonged benefit from early treatment.

Do current hypotheses on etiopathogenesis exclude prevention by early treatment?

This hypothesis of prevention is based primarily on the "remission rates" in these several trials and the contention that differential diagnosis in recent onset of inflammatory arthritis is an uncertain art in the first few months after onset. However, it is appropriate to ask whether any of the current concepts of the etiopathogenesis of RA prove it wrong. There are several proposals as to why RA develops in an individual without convincing proof of any one hypothesis[19-21].

One proposal postulates that a "precipitating event" induces disease in the preconditioned (rheumatoid factor-positive and/or anti-cyclic citrullinated peptide-positive) and genetically predisposed individual. This event includes an

external antigen that links to self-antigen on the antigen-presenting cell. When antigenic stimulation is prolonged, the susceptible individual develops an autoimmune response manifested as RA. Another proposal suggests that RA is the result of molecular mimicry. In this hypothesis cross-reactivity of a foreign antigen with a joint-structure antigen is the basis for the autoimmune response. Another proposal hypothesizes a foreign antigen disseminated and localized in joint structures. When the immune system responds to the foreign antigen, an immune complex and/or delayed hypersensitivity induces a long-lasting inflammatory response in joints.

Direct infection of the synovium has not been ruled out. Although no organisms have been consistently demonstrated in joint tissue, examples of difficult-to-demonstrate organisms, including those causing Whipple's disease and peptic ulcer, are a reminder that we cannot cultivate or demonstrate all human pathogens. None of these hypotheses excludes the possibility that RA is being prevented by early treatment with the correct combination of drugs.

Does it matter whether early treatment induces remission more frequently or prevents onset of disease? Importance of identifying the precipitating event

The possibility that we might unknowingly be preventing RA emphasizes the paramount importance of determining the nature and characteristics of the precipitating event. Clearly, if a single event is responsible for all or a very high proportion of RA onsets, we could be on the verge of successful prevention of many, perhaps most, future cases. Think of rheumatic fever. In most of the first half of the 20th century rheumatic fever was the most common cause of death for children between the ages of 10 and 15[22]. In the second half of that century rheumatic fever almost disappeared in Western countries. If multiple events are found (think of erythema nodosum), it will be more difficult but not necessarily impossible to solve the RA problem. In either case there could be a much brighter future for those who are genetically susceptible to development of RA.

Even though we have multiple agents that are effective in slowing the progression of RA, which makes life much better for newly affected patients today than even one decade ago, there are still large challenges for the active clinical investigator and the practicing rheumatologist. For young scientists in the fields of epidemiology, microbiology, infectious disease, and clinical rheumatology, the challenge of finding the precipitating event is clear.

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REFERENCES

1. Jones LR. Arthritis deformans: comprising rheumatoid arthritis, osteo-arthritis, and spondylitis deformans. New York: William Wood; 1909.
2. Fraser TN. Gold treatment in rheumatoid arthritis. Ann Rheum Dis 1945;4:71-5.
3. Lewis-Fanning E, Fletcher E. A statistical study of 1,000 cases of chronic rheumatism. Post Grad M J 1945;21:137-46,176-85.
4. Short CL, Bauer W, Reynolds WE. Rheumatoid arthritis: a definition of the disease and a description based on a numerical study of 293 patients and controls. Cambridge: Harvard University Press; 1957.
5. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo Trial Group. Lancet 1999;353:1568–73.
6. Korpela M, Laasonen L, Hannonen P, et al; FIN-RACo Trial Group. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. Arthritis Rheum 2004;50:2072-81.
7. O'Dell JR, Leff R, Paulsen G, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications. Arthritis Rheum 2002;46:1164–70.
8. Eberhardt K, Fex E. Clinical course and remission rate in patients with early rheumatoid arthritis: relationship to outcome after 5 years. Br J Rheumatol 1998;37:1324-9.
9. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum 2006;54:1401-9.
10. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586–93.
11. St. Clair EW, van der Heijde DMFM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432-43.
12. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER Study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
13. Smolen JS, Aletaha D, Keystone E. Superior efficacy of combination therapy for rheumatoid arthritis: fact or fiction? Arthritis Rheum 2005;52:2975-83.
14. van der Helm-van Mil AH, le Cessie S, van Dongen H, et al. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum 2007;56:433-40.
15. Boers M, Verhoeven AC, Markusse HM, et al.Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1998;351:220.
16. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
17. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment

strategies in patients with early rheumatoid arthritis (the BeSt Study). Arthritis Rheum 2005;52:3381-91.
18. Quinn MA, Conaghan PG, O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:27-35.
19. Harris ED, Budd RC, Firestein GS, Genovese MC, Sergent JS, Sledge CB. Kelley's textbook of rheumatology. Philadelphia: WB Saunders; 2004.
20. Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH. Rheumatology. 4th ed. Edinburgh: Mosby-Elsevier; Springer; 2008.
21. Koopman WJ, Moreland LW. Arthritis and allied conditions: a textbook of rheumatology. Philadelphia: Lippincott Williams & Wilkins; 2005.
22. White PD. Heart disease. 3rd ed. New York: MacMillan; 1944:324.

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