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RA treatment study group: Improvement in RA management

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Clinicians from North America and Europe reviewed the literature on some of the thorniest problems in the management of rheumatoid arthritis (RA). For some questions there was an emerging literature which helped us, but often there was the realization that the evidence was weak or unavailable blended with the collective experience of the group and “exceptions” learned from memorable cases and common sense and risk adversiveness that moved us forward, at least until we learned or heard better. The highlights are summarized.

1. DMARD failure: next step?

Approximately 30% of patients with RA become refractory to disease modifying agents (DMARDs) including biologics. There are theoretically 96 to 4096 combinations of 2–4 DMARDs which could be compared. Practically there are not enough resources, time or patients to study every regimen. The literature on comparative efficacy of therapeutic agents in refractory disease is scant on direct comparisons of alternatives. Studies define “refractory” RA differently, do not always distinguish those who have a side effect from those never responding, and differently from those who have a side effect to those never responding, and almost always underpowered, observational, and retrospective.

2. Defining treatment–refractory rheumatoid arthritis

The decision to change anti-rheumatic treatment because of non-response has relied on the clinical judgment of the evaluating rheumatologist. Recently there has been a movement by professional societies to recommend formal assessments of RA activity using pooled indices, such as the DAS28, and to use these indices to guide changes in treatment. Although these recommendations have not yet been widely applied, RA activity based on pooled indices was

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Conflicts of interest

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quite high at the time treatment was changed in observational studies of the addition of biologic therapy or switching among different biologics. These results suggest that rheumatologists' judgments of treatment-refractory RA in clinical practice correspond closely to the theoretical benchmarks proposed to define active RA.

Three studies suggest that titrating therapy to a quantitative endpoint is more effective than not and that the means of quantitating response and the agent is less important.

Since RA is a chronic disease, albeit with a shortened survival compared to unaffected individuals, one should make careful modifications of the current regimen unless there is a serious adverse event.

Before declaring a person as being refractory:

1. Check compliance; assess for depression especially when symptoms are out of proportion to the joint exam; re-visit previous trials of therapy and recycle old regimens;
2. Consider a trial of steroid injections of the most problematic and inflamed joints; replace activity limiting end-stage knee and hip joints;
3. Add simple analgesics including short term narcotics, NSAIDs, steroids;
4. Combine traditional DMARDS and or increase their frequency or dose. Increasing the dose of biologics is not well studied. Increasing the frequency or dose for infliximab may be necessary, for others it is not known and increasing the dose of etanercept may increase adverse events;
5. Lastly think about switching tumor necrosis factor (TNF) inhibitors and failing that switching to another biologic class.

3. How far should one “push” MTX?

The attendees discussed and then, since there are little or no published data on the subject, voted on how much to push MTX, the *de facto* standard of DMARD therapy. There was remarkable consensus that a trial of oral MTX up to 25 mg/week, in divided dose, and for a minimum of 12 weeks was a reasonable course.

4. Switching anti-TNFs or class of agent

Most studies suggest that patients with no response to one TNF inhibitor will respond to a second TNF inhibitor. Rates of response to second TNF inhibitors are lower than for TNF inhibitors naïve patients. Rituximab is efficacious in patients with RA who do not respond to TNF inhibitors. The benefit from switching to rituximab appears to be higher than switching to an alternative TNF inhibitor. Switching from antibody (infliximab or adalimumab) to soluble receptor etanercept agents is more effective than switching between two antibodies. Three studies suggest adalimumab will be more effective if the switch from infliximab was for secondary inefficacy than for adverse events.

5. Should immunomodulatory drugs be discontinued prior to elective (orthopedic) surgery?

Should the use of anti-rheumatic drugs be modified before orthopedic surgery? The literature concerning the recommendations for the use of methotrexate (MTX) (Table 1) and TNF inhibitors (Table 2) in the perioperative orthopedic setting is limited and contradictory. Whereas several studies have suggested that the continued use of MTX and TNF inhibitors in

the perioperative period may increase the risk of infection and delay wound healing, other studies have reached the opposite conclusion. The main risk of stopping these agents is that the underlying disease will flare up, requiring the use of steroids for control, which, in itself, may increase the risk of infection or delay wound healing.

5.1. Methotrexate

Earlier studies addressing this issue were generally contradictory because they were small and underpowered to show statistically significant results. The general consensus after the larger, prospective study by Grennan et al [1] is that MTX need **not** be stopped prior to orthopedic surgery in RA patients whose disease is controlled by the drug. Table 1 provides a summary of the studies published about MTX (Table 1).

5.2. TNF inhibitors

There is a similar disparity in the findings of studies investigating the safety of TNF inhibitors in the perioperative period. The contradictory findings can be explained on a number of factors, including different study populations, different definitions of drug exposures and outcome measures, and underpowered studies. Background infection rates can also vary by local factors such as hospital infection rates, surgeon skills, and patient selection criteria. Although interpretation of the following studies will not result in a uniform recommendation about the safety of continuing TNF inhibitors in the perioperative period, Bongartz et al. concluded that a policy of discontinuing TNF inhibitors will lead to an increase in disease activity in 13 patients for every 1 infection prevented, assuming a baseline infection rate of 4% and treatment with perioperative TNF inhibitors increases the risk of infection by a factor of 2. [2].

Most clinicians would consider that the morbidity, mortality, and cost of even 1 major postoperative prosthetic joint infection warrant a more conservative approach to withholding TNF inhibitors perioperatively [3]. In the absence of additional data about the safety of these agents, most groups have recommended that these agents be stopped about 4 half lives preoperatively. The half-lives of the TNF inhibitors are 8–9.5 days for infliximab, 15–19 days for adalimumab, and 100 h for etanercept.

In conclusion, MTX is generally considered safe to continue perioperatively, but caution should be exercised if significant perioperative comorbidities, like renal, hepatic, or respiratory insufficiency, develop. Data on TNF inhibitors are still inadequate to make a firm recommendation [4], but most practitioners should consider withholding these drugs for about 4 half lives prior to orthopedic surgery.

6. Can we reduce cardiovascular morbidity in RA? If so, how?

Patients with RA have a two-fold higher risk of developing coronary artery disease (CAD) compared to age- and gender-matched population. In fact, CAD is the leading cause of death in RA, accounting for over 34% of excess deaths.

Recent studies suggest that the increase in CAD and atherosclerosis in RA is not explained by the increased prevalence of traditional risk factors alone [5]. It has been suggested that the traditional risk factors act in synergy with systemic inflammation to promote atherosclerosis in RA. Inflammation at the site of vascular injury has been shown to mediate atherogenesis and an increased inflammatory burden has been linked to adverse cardiovascular outcomes in RA. Also, autopsies of patients with RA have noted increased inflammation in the walls of coronary arteries and an increase in vulnerable plaques and less severe CAD grade. This could be due to the fact that plaques in RA are more prone to rupture due to inflammation, thereby causing acute coronary events.

Current research from our group has shown that patients with RA and acute myocardial infarction (AMI) have almost same rate of mortality as patients with diabetes and AMI. However, significant declines in AMI case–fatality rates have only occurred in patients with diabetes mellitus, perhaps because of early recognition and aggressive preventive and therapeutic measures. Lesser declines in mortality rates of AMI have occurred in patients with RA. These findings have major implications for screening, early diagnosis, prevention and clinical management of CAD in patients. Patients presenting with chest pain and probable AMI should be stratified as high risk patients similar to those with diabetes and triaged accordingly.

Data from the California Medicaid program, suggests that despite an enhanced risk for CAD in patients with RA, cardio-protective use of aspirin remains inadequate at around 15%, exposing such patients to a significant risk for cardiovascular events. Wider scale risk recognition, counseling and early implementation of low-dose aspirin in patients with RA and particularly those over age 65, will be necessary to reduce cardiovascular morbidity and mortality in such patients.

Our research (Singh et al.) has also suggested that aggressive treatment of inflammation in RA, with a combination of biologic agents and MTX, can significantly reduce the risk of AMI.

There is debate about routine use of statins in individuals with normal cholesterol levels but increased signs of systemic inflammation as suggested by elevated C-reactive protein. The JUPITER study showed a dramatic lowering of CAD in such individuals treated with statins [6]. These data suggest that rheumatologists should be aggressive in their use of statins in patients with RA, even in the absence of hypercholesterolemia.

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Table 1

Evaluation of methotrexate discontinuation before surgery. Review of the literature.

Author/Type of study	References	Stop Methotrexate?
USA, Bridges et al/Observational	J Rheumatol 1991; 18:984–88	Yes
USA, Perhala et al/Retrospective	Arthritis Rheum 1991; 34:146–52	No
France, Sany et al/Prospective	J Rheumatol 1993; 20:1129–32	No
USA, Escalante et al/Retrospective	J Rheumatol 1995; 22:1844–51	No
USA, Carpenter et al/Prospective	Orthopedics 1996; 19:207–10	Yes
UK, Grennan et al/Prospective	Ann Rheum Dis 2001; 60:214–17	No
UK, Jain et al/Retrospective	J Hand Surg 2002; 27:449–55	No
Japan, Murata et al/Retrospective	Mod Rheumatol 2006; 16:14–9	No

Table 2Evaluation of anti-TNF- α discontinuation before surgery. Review of the literature.

Author/Type of study	References	Stop TNF inhibitor?
Bibbo et al/Prospective	Foot Ankle Int 2004;25:331–35	No
Wendling et al/Retrospective	Ann Rheum Dis 2005; 64:1378–79	No
Giles et al/Retrospective	Arthritis Rheum (Arthritis Care Res) 2006; 55:333–37	Yes
Ruyssen-Witrand et al/Retrospective	Clin Exp Rheum 2007; 25:430–36	Maybe
den Broeder et al/Retrospective	J Rheumatol 2007; 34:689–95	No