Welcome to the Rheumatology Highlights Report on Rheumatoid Arthritis: Non Biologic Therapy and Metrics. I’m Allan Gibofsky, Professor of Medicine and Public Health of Weill Medical College of Cornell University, and Attending Rheumatologist at Hospital For Special Surgery and New York Presbyterian Hospital. This program, together with others, is designed to give you an overview of the highlights at the recent American College of Rheumatology Annual Scientific Meeting. My topic is Non Biologic Therapy and Metrics, so let’s get right on into it. This, together with the other podcast will give you a very nice overview of the various topics of interest together with the buzz at the meeting.
The first abstract I’d like to cover is number 499 from Dhir called Efficacy and Safety of Methotrexate Starting Doses of 7.5 and 15 mg/week in Active Rheumatoid Arthritis. For many of us there is often no question about how to start Methotrexate and what dose to start it in. Most of us tend to start at the higher doses of 15 to 20 mg a week because we’re generally starting to use it in patients with more active disease. On the other hand, there are some of our colleagues who may be using it at a lower dose initially, but escalating at the same interval. The rationale being that one can get to an appropriate tolerated dose while having fewer adverse events and enhanced tolerability. So this study looks at 100 patients who had very active disease, DAS 28, three variables of 5.1 who had not been on Methotrexate, and they were divided into two groups. A starting dose of 7.5 mg per week escalated by 2.5 mg every two weeks, or 5 mg a month, or 15 mg a week escalated also 2.5 mg every two weeks, 5 mg a month. The final doses reached were 19.3 mg in the first group, 24.3 in the second. What one can see here is that there is no significant difference in disease activity and disease control at the end of 12 weeks. HAQ scores are identical; there is no difference in cytopenias, transaminitis or pneumonitis. However, the group that was started at the lower dose and escalated by 5 mg a month just as the higher dose was appeared to have much less in the way of nausea, fatigue, diarrhea and so on. So, it turns out that starting Methotrexate at a lower dose and then escalating results in better tolerability with comparable clinical control.
The next abstract, number 353, is called the The Effect of Combination Therapy and Prednisolone on Hemostatic Markers in Rheumatoid Arthritis. And, the objectives of this study were to look at whether rheumatoid arthritis should be considered a prothrombotic state. They looked at 22 patients with early rheumatoid arthritis who were randomized to either a COBRA or what they called “COBRA tight” (halved prednisone, no SSZ). PT, aPTT and other markers measured at 1, 4, 26 weeks. Baseline characteristics identical. Results: No difference in markers except for a stronger decrease in aPTT after 2 weeks in COBRA group, no longer seen at 4 weeks; similar magnitudes of decline in DAS44, CRP and ESR. Conclusions: No change in thrombotic markers with either regimen. May be possible to use even lower prednisone early. 

The next abstract, number 353, is called the The Effect of Combination Therapy and Prednisolone on Hemostatic Markers in Rheumatoid Arthritis. And, the objectives of this study were to look at whether rheumatoid arthritis should be considered a prothrombotic state. They looked at 22 patients with early rheumatoid arthritis who were randomized to either a COBRA or what they called “COBRA tight” regimen, which was ½ the dose of Prednisone received in COBRA, which you remember was a declining dose down to 10mg a week, and no sulfasalazine. They looked at the pro time, the activated partial thromboplastin time and other markers measured at 1, 4, and 26 weeks. The baseline characteristics were identical; remember this is a small cohort of only 11 patients in each group. At the end of the study, they found no difference in markers except for a stronger decrease in activated partial thromboplastin time after two weeks in the COBRA group, however this is no longer seen at 4 weeks in that group as compared to the other. There were similar magnitudes of decline in the DAS 44, CRP, and SED rate in both groups. So, the authors conclude that while there were no changes in thrombotic markers with either regimen, it may be possible to start patients out with even a lower prednisone dose earlier in the course if one is looking to start out with a COBRA like regimen that is escalation of non biologic DMARDS in the early phases of disease.
The next abstract, number 354 looks at the onset of hepatitis or neutropenia in patients with rheumatoid arthritis treated with combination therapy of Methotrexate and Leflunomide. Now, this is not a regular combination in the United States, but it is occasionally used particularly used in patients who, for one reason or another, cannot take or tolerate biologic therapy. This was a retrospective chart review of 144 patients on fixed dose MTX and 20mg of LEF for at least 6 months. What they found was the overall incidence of hepatitis was 19% (20/144). Of 144 patients, 14 (10%), 8 (6%), and 2 (1%) had delayed onset of hepatitis after 6, 12, and 24 months, respectively. The overall incidence of neutropenia was 6% (8/144). Of 144 patients, 7 (5%), 4 (3%), and 1 (1%) had delayed onset of neutropenia after 6, 12, and 24 months, respectively. The overall incidence of hepatitis was 19% (20/144). Of 144 patients, 14 (10%), 8 (6%), and 2 (1%) had delayed onset of hepatitis after 6, 12, and 24 months, respectively. Neutropenia was seen in, 7 (5%), 4 (3%), and 1 (1%) after 6, 12, and 24 months, respectively. The authors conclude that hepatitis and neutropenia may occur early or it may occur later in patients on the combination of Methotrexate and Leflunomide. Consequently, vigilant monitoring is appropriate in patients on this combination throughout the course of their regimen. I’m not sure this is an observation that is at all novel, except perhaps to come up with some crude incidence rates for hepatitis and neutropenia in patients receiving that combination.
The next abstract I’d like to look at is (slide 5) abstract 1287 by Dr. O’Dell, Methotrexate and adequate responders in rheumatoid arthritis, triple therapy vs. TNF inhibition with crossover in non responders. There has always been a question about the triple therapy data vs. the add on TNF inhibitor data in Methotrexate and adequate responders in terms of how and to what extent the three major parameters of efficacy is achieved. In other words, it does appear clear that both regimens will improve signs and symptoms. But, there had been a question as to the extent of inhibition or structural progression as compared between these two regimens. So, Dr. O’Dell did an interesting experiment by taking 353 active rheumatoids with a DAS 28 of 5.8 and a duration of 5.2 years. And, establishing that they were Methotrexate inadequate responders and randomized to add either sulfasalazine and hydroxychloroquine, the so called triple therapy combination, or they would add Etanercept on top of their Methotrexate. If the DAS 28 had not improved by at least 1.2 at the end of 24 weeks, they were switched from a strategy they were on to the alternate strategy and the primary endpoint was the DAS 28 at week 48 by the original group as well as x-rays.

The switch rate turned out to be about 27% for both groups, however at week 48 the change in the DAS was -2.1 for the triple therapy group vs. -2.3 for the group that had Etanercept added. So, in other words, there was improvement after the switch in both groups of similar magnitude. What is interesting, however, was that there was a significant difference in the x-ray progression in the group on triple therapy vs. the group that had Etanercept added. In other words, the group that had Etanercept added only showed a progression of .23 sharp scores at 48 weeks. Whereas, the group that received triple therapy had .87. And, this was statistically significant. So, the conclusion is that both strategies can achieve success, but there is a group of patients in which addition of a biologic, in this case Etanercept to Methotrexate in Methotrexate inadequate responders appeared to be better in terms of achieving a better outcome in terms of structural progression.
Now, there has been much discussion in the literature about the treat to target strategy. And, the fundamental application of the treat to target therapy is simply whatever it is that you’re using plus a metric. So, standard of care plus a metric appears to be better than standard of care alone. And, the metric could be a patient reported outcome like the rapid three, or physician defined outcome like the SLEDAI. The point is that whatever outcome is being used is less important so long as it’s guiding therapy to a particular target. Well, we know from the treat to target strategy, and we know from all the evidence from treat to target that the fundamental theorem of measurement with the strategy is better than a strategy alone. This group, Urata and colleagues, asked a question, “Well, what about if we treat to two targets? If we used aggressive initial therapy but looked at two targets?” So, this was a cohort of patients that were treated to multiple targets for a period of time extending over one year. A routine care group, a DAS 28 target of less than 2.6 target group, a group that in which matrix metalloproteinase 3 was measured, and a twin group with a DAS less than 2.6 and MM3 reducing was looked at.

So, for 56 weeks all patients were treated to both standards. At two years, there was better outcomes in the early aggressive therapy group as can be seen on the four graphs shown to the right, but there appeared to be no difference in radiographic outcome. So, there is a conundrum here as to whether routine care may not achieve the same clinical improvement but may achieve the same improvement in structural progression. And, I think that this is something that’s going to be looked at much more carefully, particularly if one looks at this abstract concurrently with Dr. O’Dell’s abstract, which I’ve just reviewed. There is no question, however, that a delay in optimal therapy may result in less better outcomes. So, the approach to the patient with early rheumatoid arthritis is optimally achieved with a strategy whether it is triple therapy or whether it is escalation of Methotrexate followed by addition of a biologic agent plus a metric. And again, it doesn’t matter whether that metric is a patient reported outcomes metric or a physician defined metric. So, there appears to be better outcomes and optimal outcomes with the strategy and a metric than the metric alone. As to whether that appears to be true when multiple targets are chosen, as to whether that appears to be true for all domains of efficacy remains to be seen.

Well, I hope you found this brief review of several significant abstracts that were presented at the ACR 2012 of interest. There is a post test view to take for your CME credit, and I encourage you to listen to the other podcasts in this series as well to get the broadest possible overview of the meeting whether you attended it or whether you didn’t attend it because there was so much information presented that I suspect that even if you did attend, much of the information being reviewed in this presentation and by my colleagues may be material that is new or perhaps a review with a different focus. This is Allan Gibofsky from the Hospital for Special Surgery, thanking you once again for your participation in this series.