Welcome to Rheumatology Highlights Report; I'm Dr. Len Calabrese from the R.J. Fasenmyer Center for Clinical Immunology. And, in the next 15 minutes I'm going to update you on the safety of biologics.
My outline today I’m going to talk about several drugs, including the newest drug that has been approved for the treatment of rheumatoid arthritis, tofacitinib. I’m going to talk about a few other complications, particularly zoster, TB and some words about vaccination. So, let’s get going; this is a tall task
Tofacitinib, what is this drug? This is the first small molecule that is the inhibitor of the intracellular JAK kinase pathway. This is a central hub that is involved in the control of numerous inflammatory cytokines. So, this functions as a biologic though it is an oral small molecule pill. What can we say about this? Is it really a drug; is it really a biologic? I will tell you my biases, it looks like a biologic and walks like a biologic.
And, the first study I show you by Kevin Winthrop talks about Tofacitinib and TB. I will just kind of highlight these slides; you can go through them and download them later. I want to make the point that this is the most robust development program of any advanced therapeutic we have in rheumatology. Nearly 5,000 patients were treated in global development programs all over the world. In this, even despite the fact that they were screened for TB, there were 12 patients that developed active tuberculosis. Not unexpectedly, these came from high incidence areas around the world, at least ten of them, four of them had extra pulmonary inseedated disease, and 11 out of 12 had negative screening tests, which only tells us that screening is not perfect. The conclusion of this study is that within the context of this large global development program, TB was rare in developed areas, like the United States, but was seen in areas of the world where there is a high incidence of TB. So, in the future as this drug now moves into the clinic patients who have a high background prevalence of latent TB or who travel and make newly acquire it are at risk.
The next slide is about opportunistic infections, and these data come from the filing information from the FDA applications. And, I only point this out, there were 33 opportunistic infections reported at that time including things such as pneumocystis, esophageal candidiasis, atypical TB, Cryptococcus, etc. These are the same type of opportunistic infections that we see in patients on other forms of biologic therapy. The rates were quite low, but it is a reminder for us to be vigilant about these types of complications.
Now, the next slide which was a study presented by Geier et al at a recent meeting in Washington compared just kind of globally the events per 100 patient years between Tofacitinib and other biologics. That includes TNF inhibitors, Rituximab, Abatacept, Tocilizumab, and it just asked three large areas: the rates of malignancies, serious infectious episodes, and serious adverse events of all types. And, as you can see, the biologics are represented by the 95% confidence intervals, and here is Tofacitinib, actually a malignancy, the global signal is actually lower, the serious infectious episode is well within the all biologic range, and the serious adverse events is slightly lower. Now, this doesn’t mean this is safer by any means, but it means that just within the mind’s eye, this is globally within the same range of the serious toxicities that we see from the standard bearers.
Now, let’s talk about zoster

- Tofacitinib
- Zoster
- Abatacept
- Tuberculosis
- Rituximab
- Vaccines
Everyone understands zoster, zoster is a dermatologic complication that is due to secondary reactivation of varicella, which in the adult population, certainly people over the age of 50 or 60 comes from their original chicken pox for people born after the mid 1990’s, they have been immunized for varicella. The disease itself is well recognized and it is a painful and morbid condition. It has the potential for complications including dissemination, post hepatic neuralgia, and even vascular effects. So, it’s a serious disease.
In the fall of 2012, the American College of Rheumatology hotline run by Jack Cush, Art Kavanaugh, I believe Kevin Winthrop was the author of this, updated us on Herpes Zoster vaccination. This is indicated for patients on non biologic DMARDS, but it is theoretically and practically contra indicated for patients on biologics. Unfortunately, patients on biologics are those that have the highest rate of zoster. So, we're left in a lurch.
So, I’d like to review with you a much discussed paper by Zhang et al in JAMA from this past summer. This is a group led by Jeff Curtis who is a noted outcomes researcher. He asked the question, “Well, there must be a lot of people out there who have inflammatory arthritis who are on biologics and who are inadvertently or explicitly given zoster vaccine.” If been occurred through primary care physicians, gone to the drugstore to get this, and so they queried a large Medicare database, they found over 4,000 patients with inflammatory arthritis. They looked within this database to see who were receiving biologics vs. non biologic DMARDs, and they found that interestingly 4% of patients had received a zoster vaccine. The bottom line of this study was that even in patients on biologics there appeared to be no adverse events in particular early reactivation or dissemination of zoster within the first six weeks and that people who did get zoster appeared to have a lower rate, zoster vaccine appeared to have a lower zoster as they moved forward. This is not an indication or an approval to give this vaccine to patients on biologics, but it’s clear evidence that we need further and prospective studies to demonstrate its efficacy.
Now, I bring, come back to Tofacitinib because this drug is kind of remarkable in one way. It has a very good infection profile, malignancy profile, but something stands out. These are data looking from the filing information before this drug was approved that was submitted to the FDA. You can see the rates for 100 patient years of herpes zoster for all Tofacitinib patients on the extreme left, and if you move this over you can compare this to placebo and to a single comparator study with Adalimumab. And, what you can see is that the rates for zoster with Tofacitinib appear higher than placebo and higher than the TNF comparator. This is present for both low and the high dose group, and so it makes it somewhat distinctive. These are actually quite high rates of herpes zoster. So, for people who are going to use this drug, we need to be vigilant about it and administer vaccines before these patients are placed on such drugs.
One of the interesting things done in further filing information shown on this slide is the effect of race, and it appears to be higher in Asians than non-Asians, and this remains unexplained.
Finally, it should be remembered that herpes zoster is not only a serious infection because it’s painful and morbid, but there are complications. However, in the Tofacitinib database, although there are patients who had serious herpes zoster and a few had complications, by and large these were kind of run of the mill herpes zoster infections.
Finally, this last slide here which looks at all major adverse events including serious infections, malignancy, lymphoma, lung cancer, myocardial infarction, perforation and herpes zoster comparing the Tofacitinib to data on TNF inhibitors and other biologics show that they are the same, except the last column, and that is herpes zoster where the rates are clearly higher. So, we need to be thinking more about this moving forward.
A few comments about some other drugs and other problems

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Abatacept, there was a nice study comparing the long term safety of subcutaneous and IV Abatacept showing both are well tolerated, both in the short term and long term. There may be some hints that there is a pharmacokinetic effect that infections might be seen a little more early than late, just like TNF inhibitors, but we need to keep our eye on this. Overall, good safety profile
A few words about TB,

- Tofacitinib
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biologics after active TB, is it possible? I mean, some patients develop pulmonary tuberculosis or extrapulmonary tuberculosis, they need to be treated. But then, the rheumatic disease comes back. Can we ever treat them again? This is a very nice study by Hernandez showing that 50 cases of active TB that ultimately were treated for this TB, 27 patients went back to TNF inhibitors after treatment and nine were actually started during treatment of TB. They all did quite well, so I think this is adding that the a pebble on the pile of safety, that this is not a lifelong contra indication.
This study by Cooray said, “How safe is treating latent TB, because we have to use INH, it’s a hepatotoxic drug, patients are on biologics, which can have hepatotoxicity. Many of them are on anti metabolites. This data in a large number of patients who were treated for latent tuberculosis show that despite our heightened concerns the combination of traditional or biologic DMARDS and INH is clinically well tolerated with only minor adverse events.
Repeat TB Testing During Biologic Therapy

- **Colorado** → low TB incidence (1.4/100K)
  - 2005-2010, 589 pts screened w/ TST before starting biologics
  - TST repeated annually (total 327 pts with 818 TSTs)
  - 9 pts converted over 5+ years; CXR neg; 8/9 completed LTBI tx; biologics continued; no active TB
- **Athens** → 50 pts w/ neg baseline TB test
  - TST, both IGRAs, CXR
  - Treated w/ anti-TNF x1 yr
  - Repeat testing: 15 (30%) converted at least 1 assay
  - No pt had concomitant conversion of >1 test
  - Further work up revealed no active TB

**Conclusions:** Repeat TB screening during biologic therapy in low-incidence areas is of questionable utility.

Finally, in TB there are two studies here looking at repeat testing, one in a low incidence area in Colorado and one in higher incidence area in TB. I’ll focus on the Athens study, this is done by my dear friend and collaborator Dimitrios Vassilopoulos, and while this is a small study, it is a disturbing study. Fifty patients in Athens who were about to start a biologic had baseline testing with skin test, chest x-ray, and both interferon gamma release assays, meaning T-spot and Quantiferon. They were put on TNF inhibitors and after a year they were retested. Inexplicably, 15, or 30% of this group converted one of these assays. In other words, they went from negative to positive. What was disturbing about it was despite the fact that they all had repeat skin tests, T-spot and Quantiferon, no patient had concomitant conversion of greater than one of these tests. In other words, it may have been a new skin test, a new T spot or new quantiferon. None of these patients as divert develop tuberculosis, so leading us to wonder, is this just the reversal of energy, a technical glitch of the test? Do these patients actually have newly exposed TB? Much more data is needed from this study, we look forward to it in manuscript form.
Finally, let’s make a few comments about Rituximab

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Rituximab has been with us for a long time. There are people that have had many, many, many rounds of Rituximab. So, the question is, “What happens when immunoglobulins become low?” This is an ongoing study and monitoring of the long term extension reported by Ron Van Vollenhoven, These were people who are on long term Rituximab which monitored every two to four months with their immunoglobulins. Then they, if they had a low isotype, M or G, then they compared the rates of infections before it was detected vs. after. I’ve noticed the fact that patients were eliminated from this study if they had low immunoglobulins at baseline.
Infection Risk in Rituximab Patients with Low Immunoglobulins

<table>
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<tr>
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<th>Pts with IgG&lt;LLN</th>
<th>Pts who never had IgG&lt;LLN (n=3082)</th>
<th>Pts with IgM&lt;LLN</th>
<th>Pts who never had IgM&lt;LLN (n=2477)</th>
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<tbody>
<tr>
<td><strong>Total PY</strong></td>
<td>223</td>
<td>11432</td>
<td>1171</td>
<td>8707</td>
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<tr>
<td><strong>Infxns, n</strong></td>
<td>325</td>
<td>9179</td>
<td>1264</td>
<td>6803</td>
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<tr>
<td><strong>Rate/ 100 PY (95% CI)</strong></td>
<td>146 (131.162)</td>
<td>80 (79; 82)</td>
<td>108 (102.114)</td>
<td>78 (76; 80)</td>
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<tr>
<td><strong>SIE, n</strong></td>
<td>18</td>
<td>425</td>
<td>34</td>
<td>339</td>
</tr>
<tr>
<td><strong>Rate/ 100PY (95% CI)</strong></td>
<td>8.06 (5.08; 12.80)</td>
<td>3.72 (3.38; 4.09)</td>
<td>2.90 (2.07; 4.06)</td>
<td>3.89 (3.50; 4.33)</td>
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Conclusions: Pts with low IgM had no increased risk of infection or SIE. For the small subgroup of pts w/low IgG, a higher SIE rate was seen both before and during/after the development of low IgG, suggesting that these pts had a higher *a priori* risk of developing SIEs.


So, here are the data in graphic form, and basically if I just point out the IgG column, if you look at the extreme right, you see the rate of infection per 100 patient years in patients who never had low IgM, and if you look in the middle you see patients who never had low IgG, rates of 3.7 to 3.8 per 100 patient years. If you look at the patients who had low IgG at any sustained period of time, the rates are 9 per 100 patient years. And, even when we looked beforehand, these people were vulnerable with rates of 8 per 100 patient years.

What does this mean to me? Well, if you look at the package insert for Rituximab, there is no requirement to monitor immunoglobulins. I will tell you that in my view, best practices are to screen for immunoglobulins at baseline, be hypervigilant of people who have low or borderline levels, and then I am repeating my immunoglobulins at the first infectious episode while patients are on this therapy. I think that we’ll see more about this in the future.
Finally, what about vaccines?

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I’ll give you two little snippets of data. One, Tofacitinib by Kevin Winthrop. He asked the question, “Can you immunize on Tofacitinib? And, do we need to stop the therapy?” This is patients who had a two week break in oral Tofacitinib, they immunized them and looked at the vaccine rates for both influenza and pneumococcal vaccine,
Tofacitinib: Vaccine Response

Conclusion: Among patients with RA, continuous tofacitinib use did not significantly impair overall responsiveness to pneumococcal and influenza vaccines, although the pneumococcal antigen GMFRs trended higher in patients who discontinued tofacitinib. A study limitation is the absence of a MTX-only control group or group lacking tofacitinib exposure. These data suggest that it is not necessary to discontinue tofacitinib in order to attain meaningful responses to pneumococcal and influenza vaccines.


and basically found no difference in the rates of vaccine response between keeping the Tofacitinib going vs. a two week holiday. Unfortunately, there is no comparator group, so we don’t really know what these rates mean, they look kind of in the ball park, much more to come
Finally, a very, very nice study by Bing Bingham from Hopkins looking at the influence of Tocilizumab on vaccine rates. This looked at both a T cell dependent tetanus toxoid and a T cell independent pneumococcus vaccine in a randomized control trial of Methotrexate vs. Methotrexate plus Tocilizumab.
The bottom line for this study is shown for the pneumococcus on this histogram showed that quite clearly Methotrexate plus Tocilizumab is associated with a palpable reduction in the frequency of sero type conversion and thus I think we add this to our biologics such as Rituximab we really should probably strategize to vaccinate before we start this drug. There was much less effect on tetanus toxoid.
So, I'll give this conclusion is that we need to be vigilant.

So, finally I think I've given you a high altitude view of some of the new drugs and some of the old problems. I'd like to welcome you to come back to RHR, and this is my crew. There are many other great presentations, and in 15 minutes we will give you the world of rheumatology.