

Could Cholesterol Increases be Good for Actemra and Tofacitinib?

Companies:

Pfizer (PFE)
Roche (OTC: RHHBY)
Amgen (AMGN)
Abbott (ABT)
Johnson & Johnson (JNJ)
Bristol-Myers Squibb (BMY)

Products:

Actemra (tocilizumab)
Tofacitinib (phase III)
Enbrel (etanercept)
Humira (adalimumab)
Orencia (abatacept)
Rituxan (rituximab)

The *inThought* Approvability Index (IAI)

uses historical approval rates and detailed analysis of clinical trials to model the probability of approval. The letter grade indicates relative progress in the current phase — in Eliquis's case, reflecting a considerably greater than average probability of advancing to regulatory review.

- The side effect of raising LDL and other lipids has held back sales of Roche's (OTC: RHHBY) Actemra (tocilizumab) for rheumatoid arthritis (RA), and is likely to impact use of Pfizer's (PFE) tofacitinib.
- But studies suggest that the kinds of lipids associated with by IL6 and JAK inhibitors such as Actemra and tofacitinib may actually benefit RA patients. Compelling data were presented at recent meeting by Professor Iain McInnes.
- Long-term cardiovascular outcome studies are needed to answer this question. Such studies are expensive and time consuming.
- Aside from the cholesterol issue, Actemra will face competition from IL6 inhibitors in development from Sanofi/Regeneron, Bristol-Myers Squibb, Johnson & Johnson, UCB, and others.
- Tofacitinib is on track to become the first oral kinase inhibitor approved for RA. Its challenge will be to displace TNF inhibitors as a "first-line" drug for methotrexate refractory patients.
- Actemra worldwide sales were \$425 million in 2010, and *inThought* projects revenue that remain in the \$300-\$500 million range through 2018.
- Tofacitinib has an 81%(A) *inThought* Approvability Index (IAI). We model peak worldwide revenue of \$1.75 billion in 2017.

Drug development for severe rheumatoid arthritis (RA) has been one of the most successful and lucrative areas of drug development over the last 15 years. Currently, nine biologics are approved for the treatment of patients who are refractory to methotrexate and other oral disease modifying anti-rheumatic drugs (DMARDs). Those nine drugs generate over \$16 billion in worldwide sales each year for various autoimmune conditions, approximately $\frac{3}{4}$ of which is due to use by RA patients.

Five the drugs are TNF inhibitors used as “first-line” therapy for those patients failing oral DMARDs:

- **Enbrel** (Amgen and Pfizer)
- **Humira** (Abbott)
- **Remicade** (Johnson & Johnson)
- **Cimzia** (UCB)
- **Simponi** (Johnson & Johnson)

For patients who respond inadequately to TNF inhibitors (TNF-IR), rheumatologists have four options:

- **Orencia** (Bristol-Myers Squibb; T cell co-stimulation inhibitor)
- **Actemra** (Roche; IL6 inhibitor)
- **Rituxan** (Roche and Biogen Idec; B cell depletor via CD20)
- **Kineret** (Amgen and Biovitrum, IL1 inhibitor, rarely used).

Impact on lipids is likely an intrinsic effect of both JAK and IL6 inhibitors.

Actemra is the most recently approved of these agents, generating \$425 million in worldwide sales in 2010. It primarily competes with Orencia and Rituxan, but Roche hopes that it will move into the first-line biologics setting as a competitor to TNF inhibitors.

RA Pipeline

Given the large revenue potential of RA drugs, it is not surprising that drug development is active. The most promising class of new drugs is the oral kinase inhibitors, which hold the hope for efficacy and safety similar to biologics with the convenience of a once or twice daily pill. Pfizer’s JAK inhibitor tofacitinib is the most advanced of these agents. Its robust phase III program has generated promising results, and the drug will be the hot topic at this year’s American College of Rheumatology (ACR) meeting in Chicago in early November.

Behind tofacitinib are several other oral kinase inhibitors, including Rigel and Astra Zeneca’s SYK inhibitor fostamatinib (beginning phase III) and two phase II JAK inhibitors, one from Vertex and one from Lilly/Incyte.

At least thirty biologics are in clinical trials for RA, including seven IL6 inhibitors that, if approved, will compete directly with Actemra. IL6 inhibitors beginning phase III or completing phase II are being developed by Bristol-Myers Squibb / Aldor, UCB, Johnson & Johnson, and Regeneron / Sanofi.

Lipid Levels with IL6 and JAK Inhibitors

Rheumatology experts are excited about the potential of Actemra, and would like to use it more frequently in TNF-IR patients. It typically acts faster than Orencia and is at least perceived to be safer than Rituxan. However, these experts cite increases in LDL cholesterol and other lipids as an issue that has held back perscription of Actemra, especially with community physicians.

Trials of tofacitinib and other JAK inhibitors have shown similar, although perhaps milder, increases in the same lipids. It is thought that JAK inhibition decreases signaling through the IL6 receptor, and that the impact on lipids is an intrinsic effect of both JAK and IL6 inhibitors.

LDL and related lipids are subclinical markers for heart disease, and therefore the real question is whether patients taking Actemra or tofacitinib are at greater risk for a heart attack or other cardiovascular events. Here the issue gets interesting, with what can be perceived as a clear divergence of medical evidence vs. physician perception.

There is no good evidence that Actemra or tofacitinib increase the risk of cardiovascular disease (CVD). Analysis is complicated by the fact that RA itself increases the risk of CVD, and therefore drugs that control RA should lower CVD risk (Sattar and McInnes, “Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions”, *Current Opinion in Rheumatology*, May 2005, 17;3,286-292). The degree to which RA drugs such as TNF inhibitors lower CVD risk is difficult to measure even without consideration of a confounding impact on cholesterol levels and even with a decade of experience with hundreds of thousands of patients.

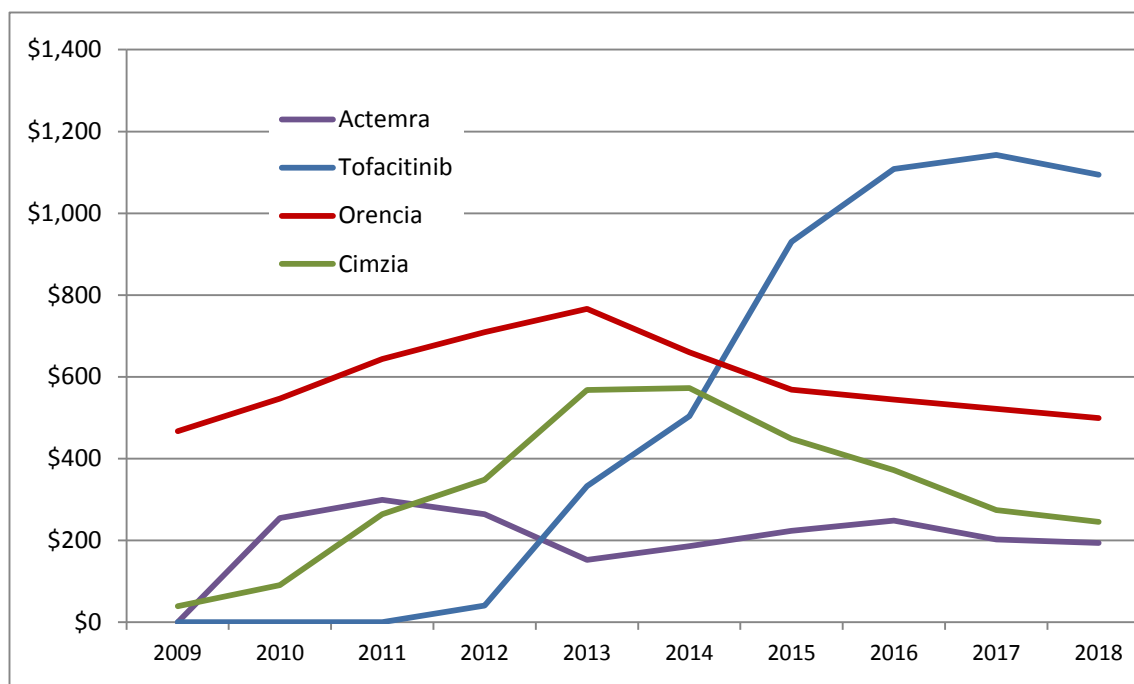
At the ACR meeting last year as well as the European League Against Rheumatism (EULAR) meeting this year, Professor McInnes presented some basic science work that challenges the idea that all cholesterol is bad. His lab used nuclear magnetic resonance (NMR) spectroscopy to analyze the species of LDL, HDL, and other lipids that are found in people treated with Actemra, finding that not only was HDL (well-known good cholesterol) increased, but that even the forms of LDL associated with IL6 were less likely to lead to CVD, suggesting that these are “anti-inflammatory” LDL and other lipid species produced (McInnes et al, “Measure: A Translational, Randomized, Placebo (PBO)-Controlled Study To Evaluate The Effects Of Tocilizumab (Tcz) On Parameters Of Lipids And Inflammation” presented at EULAR 2011). For lipid aficionados, the research showed that Actemra raised levels of large, more buoyant subclasses of LDL while leaving small, dense LDL particles unchanged. Though some of the less well-known LDL, and related marker, subclasses have received

some attention, many experts believe that the bench to bedside to bench work now demanded by the emerging RA market will lead to unprecedented target validation discovery in both autoimmune and cardiovascular therapeutic areas.

Although intriguing, McInnes’ work certainly does not show that Actemra has a beneficial effect on CVD risk. For that, long and expensive cardiovascular outcomes studies are needed.

The first of those studies is now underway. Roche has initiated a 5½-year study seeking to enroll 2800 RA patients to compare the rate of ischemic cardiovascular events seen with Enbrel versus Actemra. Although they applaud the study design, rheumatology experts are not optimistic that a clear answer will emerge from the trial. Most likely, they say, the trial will show that Actemra and Enbrel are associated with similar rates of CVD; detection of differences will be difficult.

Figure 1: U.S. Revenue Forecasts for Actemra, Tofacitinib, Orencia, and Cimzia



Source: inThought estimates, company data

Real-World Implications

The net result of the evidence for and against increased CVD risk with Actemra and tofacitinib is uncertainty. In clinical practice, physicians choosing between these agents and TNF inhibitors are aware of potential increases in cholesterol, and that this increase may or may not be associated with a small change (either positive or negative) in cardiovascular health. Definitive answers will not emerge until 2016 at the earliest.

We believe that, faced with a choice between the known safety and efficacy profile of TNF inhibitors and the uncertainty associated with Actemra, physicians and patients continue to will favor TNF inhibitors. The cholesterol issue remains one of many factors that will make TNF inhibitors difficult to displace as the first-line option for methotrexate inadequate responders, both for Actemra and other IL6 inhibitors as well as for tofacitinib and other JAK inhibitors.

Actemra Forecast

In its quest to find use as a first-line alternative to TNF inhibitors, Actemra faces multiple threats. While its efficacy and safety appear to be on par with TNF inhibitors, it is currently available only as an intravenous (IV) infusion, typically less popular with patients than the subcutaneous (SQ) formulation of Enbrel and Humira.

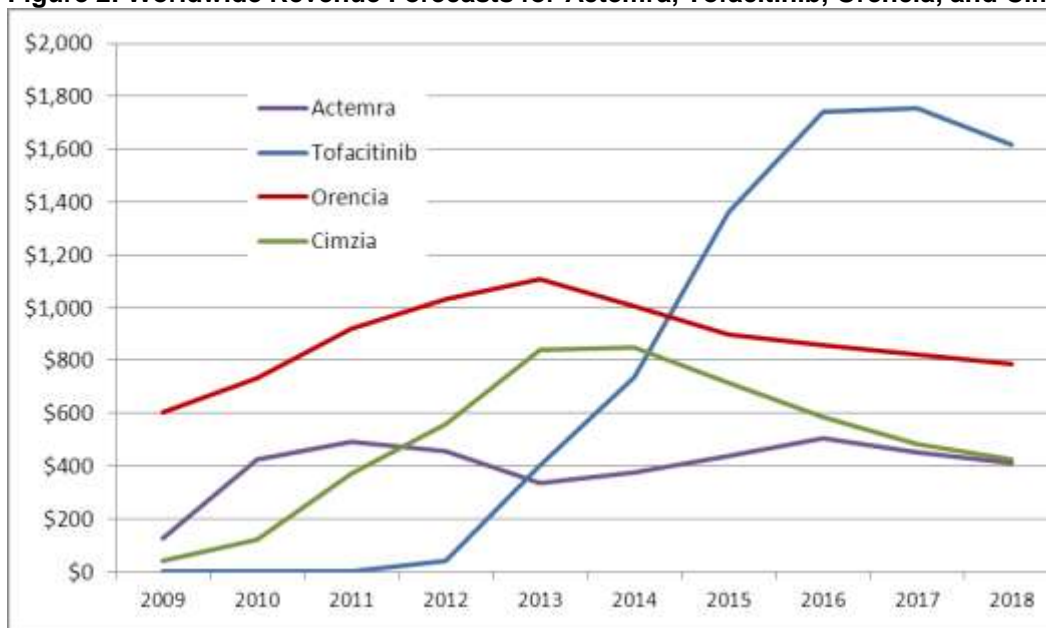
Even in the TNF-IR market, Actemra will face competition now from SQ Orencia, which was approved in July. We expect SQ Orencia to gain market share from Actemra and Rituxan due to its SQ formulation in the short term (see *inThought Research*, September 9, 2011: “*Subcutaneous Formulation Will Expand Orencia’s Market*”). Roche is also developing a SQ formulation of Actemra, which our model assumes is available in 2014.

Actemra faces direct competition from other IL6 formulations. Our model assumes that other IL6 inhibitors are similar to Actemra in terms of safety and efficacy, but it is possible that differences such as binding to IL6 rather than to its receptor will give other compounds an advantage over Actemra. The SQ formulation of Actemra is key to competing with new IL6 inhibitors, which are all being developed as SQ formulations.

Actemra’s greatest threat is ultimately tofacitinib and other oral kinase inhibitors. Whether IV or SQ, it will be difficult for Actemra to compete with an oral agent in the TNF-IR market.

Figures 1 and 2 show worldwide sales from Actemra (SQ + IV) dipping in 2012 and 2013 before stabilizing after the SQ formulation is introduced. The drug never breaks out of the \$500 million worldwide sales range in our model.

Figure 2: Worldwide Revenue Forecasts for Actemra, Tofacitinib, Orencia, and Cimzia



Source: *inThought* estimates, company data

Tofacitinib Forecast

In addition to the uncertainty of its impact on cardiovascular health, tofacitinib faces other safety issues. The serious infections and deaths observed in the phase III program will make it difficult for rheumatologists to choose tofacitinib over a TNF inhibitor, not because it's necessarily less safe, but because TNF inhibitors are a known quantity with over a decade of safety data.

On the efficacy side, tofacitinib looks at least as good as TNF inhibitors. More details will be available when the head-to-head data compared to Humira are presented at ACR in a few weeks.

We assign an 81%(A) IAI to tofacitinib. Significantly more data will be presented and discussed at ACR. We assume a late 2012 FDA approval based on filing in late 2011 with modest delays.

Our revenue model assumes that tofacitinib quickly captures the bulk of the TNF-IR market, competing

effectively against Actemra, Orencia, and Rituxan. Over time, and accelerating after 2014, we assume modest penetration of the first-line market currently held by TNF inhibitors. Figures 1 and 2 show U.S. and worldwide revenues increasing \$1.1 and \$1.7 billion, respectively, at peak in 2017 before facing competition from other oral kinase inhibitors and biosimilar TNF inhibitors.

One potential upside to our model for tofacitinib is revenue from emerging markets (outside the U.S., EU5, and Japan). TNF inhibitors are not widely used in China, India, and other emerging markets, so an oral drug such as tofacitinib will have a large opportunity to become a default choice. Pfizer's decisions on pricing the drug, especially in emerging markets, will be key. For the U.S., we assume a 30% discount to the nominal price of TNF inhibitors, or approximately \$10,000 per patient per year after discounts and rebates and accounting for compliance.

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