NEWS

Denosumab and the Treatment of Rheumatoid Arthritis: In an Occupied Field, Where Will a RANKL Inhibitor Fit In?

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In treating patients with rheumatoid arthritis (RA), physicians have two goals: control the clinical signs and symptoms, such as joint pain and swelling, caused by the inflammation underlying the disease, and slow the bone erosions and joint damage that may subsequently develop. In this regard, the RA field is quite fortunate, since therapies are now available that achieve both aims. A brief consideration of current treatments for RA bears this out.

Initially, most RA patients are treated with methotrexate or another disease-modifying antirheumatic drug (DMARD). As the name suggests, these agents alter the underlying disease process of inflammation that drives RA, and can be quite effective in relieving both the clinical signs and symptoms of the disease and bone erosions. Yet many patients on methotrexate or other first line, non-biologic DMARDs continue to experience problems with bone erosions even if their disease is well-controlled clinically. The next step for such patients is to try one of several anti-TNF-α agents. These biologics, such as etanercept, infliximab and adalimumab, have proven effectiveness in treating both inflammation and bone erosions by inhibiting TNF-α, an important cytokine implicated in RA. In fact, about 70% of patients taking these agents respond to them. For the 30% who don't, the RA field can even then turn to two other approved biologic DMARDs that help both with disease activity and bone erosions, namely abatacept and rituximab; the former works by inhibiting the activation of the immune system's T cells, while the latter functions by reducing the number of B cells.

Into this seemingly crowded terrain may soon emerge another entry: denosumab. A monoclonal antibody developed for both osteoporosis, RA, and other conditions, denosumab works via a mechanism different from that of the other biologics currently approved for the treatment of RA. Specifically, it inhibits the osteoclast by binding to RANKL, a molecule that upon binding to its receptor, RANK, on the surface of osteoclast precursors, normally stimulates the differentiation, activation and survival of osteoclasts. Yet, unlike biologics like TNF inhibitors, denosumab does not impact the inflammatory disease activity of RA but rather appears only to ameliorate bone erosions. In fact, in phase II results published earlier this year (1), investigators studied RA patients who continued to have active, erosive disease despite taking methotrexate. They found that adding denosumab to the patients' treatment resulted in smaller increases in bone erosion scores as measured by MRI and by X-ray, compared to placebo subjects taking just methotrexate, but did not produce any changes in underlying inflammatory disease activity.

However, if the goal is both to improve the clinical signs and symptoms of RA and to prevent bone erosions and joint damage, and currently available treatments already do just that – and in different ways, thus providing physicians with a variety of treatment options from a mechanistic perspective – why does the RA field need denosumab, at all?

At this relatively early stage of clinical research, where combination studies assessing whether the addition of denosumab to current treatments like TNF inhibitors provides an additional benefit to patients are lacking, as are head-to-head
studies comparing denosumab to other DMARDs, the RA field cannot yet specify exactly what role it will play in the treatment of RA. However, while the specific details remain cloudy, a rough general sketch does begin to emerge from interviews with RA experts. Since denosumab does not have an impact on disease activity, and in the face of the success of TNF inhibitors, some arthritis specialists appear decidedly unenthusiastic about the potential use of this new drug specifically for the treatment of RA. Interestingly, though, these skeptics can still envision an important role for denosumab, but for reasons that have less to do with science and more to do with the often prohibitive expense of TNF inhibitors. On the other hand, some experts, including those who have participated on denosumab research but also outside experts, are in fact encouraged about denosumab’s potential use in particular subpopulations of RA patients for whom current treatments are insufficient. Much of the excitement, however, that RA experts have for denosumab is reserved for its potential to treat, at the same time, both RA and the osteoporosis that often accompanies RA. Here too, though, denosumab will have to compete with current therapies.

A Complement to Standard DMARDs

RA experts agree that because denosumab does not affect inflammation and the clinical signs and symptoms of RA, it will never be a stand-alone, first-line treatment for RA. Rather, denosumab will need to be given in combination with a DMARD; this is the first potential future use that some experts foresee for the drug. In particular, some specialists envision administering denosumab with methotrexate, or another DMARD like leflunomide or sulfasalazine, specifically for those patients who continue to progress with bone erosions despite exhibiting good clinical responses.

“About one-third of patients who do well clinically on methotrexate continue to progress and have joint damage and deformity. We originally thought we were doing a great job with these patients, but the majority of them still went on to develop damage,” explains Stanley Cohen, first author of the denosumab phase II study and medical director of Metroplex Clinical Research Center in Dallas, Texas. Using denosumab for patients on DMARDs who still experience problems with bone erosions despite good clinical improvement could prove helpful for patients who are satisfied with the status quo but whose doctors are not, according to Atul Deodhar, an associate professor of medicine and director of the rheumatology clinic at Oregon Health & Science University in Portland and a member, of the Denosumab RA Study Group, who served as a clinical investigator for the phase II study. “There are patients I see who are doing well clinically and who say they are happy with their progress and don’t want to change anything, but you as the doctor are unhappy because the X-ray has changed and has revealed that new erosion has occurred,” says Dr. Deodhar. “I see a niche for denosumab in that group of patients.”

While the phase II study examined the effects of denosumab in patients who already had erosive RA, experts suggest that future clinical trials should test the drug much earlier, in patients who don’t yet have bone erosions, to see if denosumab could prevent the erosions from occurring in the first place.

Why Not Just Give Anti-TNF Inhibitors to Everyone?

However, for patients taking DMARDs like methotrexate who continue to struggle with bone erosions, anti-TNF therapies are already available and are extremely effective. In fact, some RA experts mention that these inhibitors are so powerful that they stop bone erosions even in those who fail to exhibit symptomatic improvement in their disease. This high success rate has led Edward Schwarz, a professor of orthopaedics at the University of Rochester in New York, to be skeptical of denosumab’s potential use in treating RA.

“From a scientific perspective, there is no reason that I can think of why you would treat an RA patient with an anti-RANKL
agent,” asserts Dr. Schwarz, who has written extensively about the clinical development of anti-RANKL therapies. “70% of patients respond to anti-TNF therapy – that's a pretty big home run,” he stresses.

If TNF inhibitors are so effective, why not just administer them to every RA patient who could benefit? Dr. Schwarz and other experts emphasize the reality that TNF inhibitors are extraordinarily expensive, easily costing roughly 15,000 dollars per year or more. “For those that can't afford 15,000 dollars a year, for life, for anti-TNF therapy, what are you going to give them? If it's true that 1-2% of the population has RA, there is no economic model that posits putting all of those people on a therapy that costs 15,000 dollars a year, for life,” says Dr. Schwarz. The “politically incorrect” answer, according to Dr. Schwarz, to the question of why the RA field needs denosumab at all is simply that anti-TNF therapy costs far too much, for too many patients.

The problem of the expense of TNF inhibitors is widely recognized by RA specialists. In fact, strikingly, in recent recommendations from the American College of Rheumatology (ACR) (2) regarding the use of non-biologic and biologic DMARDs in RA, alternate recommendations for patients for whom “cost or insurance coverage limitations” rule out the use of expensive biologic DMARDs were provided. In an editorial on the recommendations, Dr. Cohen and a colleague even wrote that “the fact that such a modification is needed is a sad commentary on our broken health care system” (3).

Consequently, whether denosumab becomes a prominent treatment in the RA field will depend on its price. “If Amgen pitches this drug at, say, 1,000-1,500.00 dollars a year, that would create a stir in the rheumatology community. It will lead us to rethink, why are we using anti-TNF therapies if we can just manage patients with methotrexate and denosumab,” Dr. Deodhar says.

Treating patients with just a DMARD and denosumab instead of TNF inhibitors – is this actually feasible in clinical practice? One possibility is that, while denosumab does not impact RA disease activity, it does work against what RA physicians fear the most, potentially allowing the drugs that do impact disease activity to do a better job. “Rheumatologists worry about structural change and joint damage, and that's one of the arguments for early and aggressive use of biologics,” explains Philip Sambrook, a professor of rheumatology at the University of Sydney in Australia. “If you have a biologic like denosumab that was substantially cheaper and that prevented radiographic progression, then people may well persist with some of the other anti-inflammatory or disease-modifying agents that are cheaper, knowing they've got time to control the disease since joint structure won't change so quickly.”

If future clinical trials could establish that patients could in fact be managed without TNF inhibitors, experts say there is definitely a market opportunity here for denosumab because of the daunting cost issues. “In some countries, regulatory authorities are very strict on TNF blockers,” says Georg Schett, an expert on the molecular mechanisms of inflammatory bone damage and a professor at the University of Erlangen-Nuremberg in Germany. “For instance, in Europe, on average, only 10-20% of RA patients are on TNF blockers, so you can imagine that there is a market for a drug like denosumab on top of methotrexate,” according to Dr. Schett. Also creating a market for denosumab is the actuality that some patients do not want to take any anti-TNF drugs in the first place because they fear side effects of these powerful agents.

Helping Patients Already Taking TNF Inhibitors

But what about patients already on TNF inhibitors – are there any potential uses for denosumab in that group? Experts say yes. First, individuals responding well clinically to TNF inhibitors may be able to stop taking them. “There are patients we may be able to
wean off of the TNF blockers and preserve joint structure using denosumab,” according to Nancy Lane, a professor of medicine and rheumatology at the University of California, Davis Medical Center in Sacramento, and an author of the phase 2 study.

Second, despite TNF inhibitors’ effectiveness, there are still some patients for whom these therapies are insufficient in terms of preventing bone erosions. “Denosumab is highly unlikely to affect the signs and symptoms of RA, so in that sense it is not an appropriate therapy for RA. But it will very likely slow bone erosion, and since we know that there is continued bone erosion in 15% of patients who are using TNF blockers, there is a place for this drug in that group of patients,” says Daniel Furst, a professor of medicine and rheumatology at the University of California, Los Angeles and senior author of the ACR recommendations.

One of the options for such patients is to add denosumab to their anti-TNF therapy. Some experts, though, strongly question the wisdom of this approach, as it entails the combination of two biologic drugs. “Anti-TNF agents are so powerful, they completely stop X-ray progression, so adding denosumab to anti-TNF is a waste of time and a significant waste of money,” Dr. Deodhar asserts. Dr. Deodhar acknowledges that there are some patients who continue to have trouble with bone erosions even with TNF inhibitors, but says that in such cases, he would take patients off of the TNF inhibitors completely and only use denosumab. His and other experts’ primary concern about combining 2 biologics is about possible increases in infections. “There is not a single study that I know of that has demonstrated the safety of using two biologics together,” he emphasizes. However, Dr. Sambrook notes that, thus far, denosumab, with its unique mechanism of action, does not appear to have resulted in increases in infections. Most of the experts interviewed for this article expressed little concern about potential immune system side effects of denosumab, saying that the data thus far give little cause for concern in that regard.

Treating Two Diseases At Once

While RA experts envision a role for denosumab for those who cannot afford TNF inhibitors and in specific subpopulations of RA patients, what they appear more excited about is its future role as a combination treatment that fights not just RA but, at the same time, the osteoporosis that often accompanies RA. Many RA patients take glucocorticoids, for instance, which increase the risk of osteoporosis, and of course many RA patients are older, postmenopausal women at increased risk of the disease. RA itself is a risk factor for osteoporosis and is included in the FRAX® algorithms for fracture risk assessment.

“The positioning of denosumab, should it be approved for use, particularly in osteoporosis, would be the potential to use it in many of our RA patients who are concomitantly on glucocorticoids, or who have other risk factors for osteoporosis, where there would be a benefit in terms of fracture risk reduction, concomitant with a benefit in potentially suppressing the progression of their bone erosions,” according to Kenneth Saag, a professor of medicine and epidemiology at the University of Alabama at Birmingham, and first author of the ACR recommendations. Dr. Saag estimates that about one-third of RA patients take glucocorticoids.

Of course, bisphosphonates are already available to treat osteoporosis. Why would it be preferable to use denosumab, instead of a bisphosphonate, to treat an RA patient’s osteoporosis? RA experts say that doing so will allow them to accomplish two goals at once: to treat osteoporosis, but also bone erosions, simultaneously, since oral bisphosphonates have not been found effective in treating the latter.

“What I feel is most important about denosumab is that it treats two conditions that are both related to RANKL,” explains Robin Dore, a clinical professor of medicine at the David Geffen School of Medicine at UCLA and one of the authors of the phase II study. “So now my patients, instead of
taking a bisphosphonate, should be able to take just denosumab which, in combination with another RA drug, will help both their RA and their osteoporosis. It's the advantage of treating the two diseases, rather than the fact that it just reduces bone erosions in RA, that's going to make it such an important therapy for our patients,” says Dr. Dore, who also notes that another advantage to denosumab is its convenient dosing of once every six months, which may appeal to patients looking for simplicity in their treatment.

Here too, though, denosumab could potentially face competition, in this instance from zoledronic acid. While oral bisphosphonates have not been found effective for treating RA bone erosions in humans, perhaps because doses have not been high enough to produce any changes, one small study of 39 patients with early RA who were taking methotrexate did find an effect of intravenous zoledronic acid: patients who received this powerful bisphosphonate exhibited a 61% decrease from baseline in MRI bone erosion scores, compared to those taking only methotrexate, though this finding was not statistically significant (4). However, some experts point to the small size of the study and emphasize that it provides proof-of-concept data, rather than definitive proof. Consequently, without more convincing studies, it remains difficult to gauge exactly how strong a competitive challenge zoledronic acid may ultimately pose to denosumab in instances where doctors seek to treat both RA bone erosions and generalized osteoporosis.

An Uncertain Future

From a scientific vantage point, questions do remain regarding denosumab’s impact in RA. For instance, the phase II study found that denosumab did not affect joint space narrowing, which reflects cartilage destruction. This could be because higher doses are needed to produce a chondroprotective effect, or, on the other hand, denosumab may just not affect the chondrocyte. In the phase II study, the authors also noted that there isn’t a lot of evidence suggesting the relative importance of protecting cartilage versus protecting bone. Most of the currently approved DMARDs for RA appear primarily to prevent bone erosions rather than cartilage destruction, though this could be because it is difficult to measure changes in cartilage with X-rays, while MRI, which can better visualize cartilage, has not yet been used extensively for that purpose in RA.

As the field tries to work these issues out, it is clear that denosumab, if approved for the treatment of RA, will have to make its own way amongst current treatments that already accomplish what it does and more. The future will also bring new competitors, including agents targeting other cytokines implicated in RA. Nevertheless, the advent of a new drug like denosumab, even in a field crowded with treatments, is not a bad thing for a disease like RA. Indeed, so many different factors – a multiplicity of cytokines and signaling molecules – have been implicated in RA, and which of these factors is most important may differ from patient to patient. Because of this, there is no one agent that will serve as a holy grail that is suitable for each and every patient.

“RA likely represents a heterogeneous group of conditions with a similar phenotype. The manifestations in individual patients can vary considerably. Much of our therapy, while similar for most patients, needs to be individualized to some degree, based on the aggressivity and disease characteristics of a given patient,” says Dr. Saag. With a disease of this nature, a drug with a new mechanism may still be valuable, even if it overlaps with current treatments. Nevertheless, until more clinical trial data become available, it’s unclear whether the predictions of RA experts regarding denosumab’s future place in RA treatment will come true.

“I'm intrigued about denosumab's mechanism of action as being quite unique in the rheumatoid arthritis setting, but I'm unclear about how it's going to fit into clinical practice, given the trial data we have to date,” says Dr. Sambrook, expressing a sentiment with which many RA experts would agree.

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References


Conflict of Interest: Authors/investigators from the phase II study include Dr. Cohen, who is a consultant for Amgen; Dr. Deodhar, who has not received any financial support from the company; Robin Dore, who is on the speaker’s bureau for the company; and Dr. Lane, who does not speak or consult for Amgen, while the University of California did contract research for the company. Dr. Furst, Dr. Saag, Dr. Sambrook, Dr. Schett and Dr. Schwarz were not involved with the denosumab trial.