

Rheumatology

Few autoimmune competitors even come close to commercial stalwarts Humira, Enbrel and Remicade. But as a host of high-science treatments emerge seeking to threaten their reign, an old-fashioned and heretofore illicit drug could beckon patients to look beyond traditional medicines for rheumatology relief. **Joe Dysart** surveys the sector

Ironically, one of the biggest new competitors in the rheumatology market is not some wunderkind upstart with a dazzling, magic pill. Instead, it's your friendly, local drug dealer who sells pot.

Indeed, more than a few players in rheumatology are concerned that the growing acceptance of marijuana as a medicinal — and even recreational drug — across the US could prompt untold numbers of patients to seek out pot sellers for rheumatology relief, rather than the traditional medical community.

“Physicians caring for patients who are self-medicating with marijuana need to understand the health implications of using this drug,” says Dr. Mary-Ann Fitzcharles, a rheumatologist at McGill University Health Center in Quebec, and a researcher on a March study critical of medicinal marijuana.

“At this time, we cannot recommend herbal cannabis for arthritis pain management given the lack of efficacy data, potential harm from the drug, and availability of other therapies for managing pain,” says Fitzcharles. “Physicians should discourage rheumatology patients from using medical marijuana as a therapy.”

Fitzcharles's study, “Arthritis Care & Research,” released in March, found that the THC in pot negatively impacts cognitive and psychomotor function, and that long-term use may lead to mental illness, dependence, addiction and memory impairment.

Simultaneously, 20 states in the US, along with the District of Columbia, have already legalized marijuana for medical treatment — a trend expected to lead to even more states legalizing pot in coming years.

Marijuana's momentum

Part of the momentum behind medicinal marijuana, and its growing acceptance over more traditional treatments for rheumatology ailments, is that some very respected medical authorities are getting behind THC.

CNN's Dr. Sanjay Gupta, for example, reversed his stance on



pot last year, and is now a strong supporter of the drug for certain treatments. “I think we’ve been terribly and systematically misled,” about medical marijuana, Gupta says in his CNN documentary, “Weed 2,” who adds that the drug can “work wonders.”

Meanwhile, in the traditional medications market for rheumatology, all eyes are on Humira, a treatment for rheumatoid arthritis, psoriasis, Crohn's disease and other ailments, which is also the world's top-selling drug, according to market research firm Evaluate in its report World Preview 2013, Outlook to 2018.

Humira competes with the world's second-most popular drug, Amgen's Enbrel, which is still sold by Pfizer in some ex-US markets, and Janssen/Merck/Mitsubishi Tanabe's Remicade, the world's third-most popular drug, according to Evaluate.

The problem for Humira, made by AbbVie, is that its patent protection expires in late 2016, triggering uncertainty about how long the powerhouse will continue to dominate the sector.

Laura Wood, a senior manager at Research and Markets, predicts Humira will likely retain the lion's share of the market through 2022—

TOP 30 RHEUMATOLOGY PRODUCTS, 2013

Category leaders, ranked by US sales and their media spend

Rank	Product	Manufacturer	US sales \$ (millions)	Vs. prior 12 months	TRx (000s)	Vs. prior 12 months	US DTC media \$ (millions)	Vs. prior 12 months	US journal media \$ (millions)	Vs. prior 12 months
1	Humira	AbbVie	\$5,566.0	24.0%	1,852.0	9.0%	\$290.6	47.0%	\$3.8	2.1%
2	Cymbalta	Eli Lilly	\$5,278.1	14.0%	1,857.3	0.0%	\$120.0	-51.0%	\$0.0	N/A
3	Enbrel	Amgen	\$4,710.8	12.0%	1,635.0	0.0%	\$128.2	-24.0%	\$1.6	3.6%
4	Remicade	Johnson & Johnson	\$4,114.7	7.0%	77.0	-2.0%	\$0.0	N/A	\$0.0	-100.0%
5	Copaxone	Teva	\$3,711.1	6.0%	668.0	-6.0%	\$0.0	N/A	\$0.7	-1.3%
6	Rituxan	Roche/Biogen	\$3,298.1†	5.0%	9.0	7.0%	\$0.0	N/A	\$0.5	N/A
7	Lyrica	Pfizer	\$2,454.7	24.0%	9,448.0	4.0%	\$170.3	25.0%	\$4.8	-25.2%
8	Celebrex	Pfizer	\$2,269.7	17.0%	9,098.0	-3.0%	\$150.0	16.0%	\$0.0	N/A
9	Rebif	Pfizer/Merck KGaA	\$1,274.0	4.0%	252.0	-18.0%	\$0.0	N/A	\$0.0	-100.0%
10	Avonex	Biogen Idec	\$1,245.5	-25.0%	238.0	-33.0%	\$0.0	N/A	\$0.9	-2.3%
11	Gilenya	Novartis	\$1,060.5	26.0%	166.0	16.0%	\$27.5	>100.0%	\$0.7	-12.1%
12	Stelara	Johnson & Johnson	\$966.1	43.0%	94.0	28.0%	\$20.4	-24.0%	\$0.2	-48.0%
13	Orencia	Bristol-Myers Squibb	\$960.1	19.0%	149.0	53.0%	\$40.3	-25.0%	\$0.7	-51.6%
14	Tecfidera	Biogen Idec	\$880.0	N/A	135.0	N/A	\$0.0	N/A	\$1.3	N/A
15	Evista	Eli Lilly	\$829.9	8.0%	2,941.0	-12.0%	\$0.0	-100.0%	\$1.3	-14.6%
16	Betaseron	Bayer	\$812.6	1.0%	149.0	-17.0%	\$0.0	N/A	\$0.0	-100.0%
17	Avonex Pen	Biogen Idec	\$771.2	>100.0%	145.0	>100.0%	\$0.0	N/A	\$0.9	-2.3%
18	Pristiq	Pfizer	\$643.8	12.0%	3,217.0	-9.0%	\$44.0	52.0%	\$0.6	-9.0%
19	Lialda	Shire	\$560.6	28.0%	814.0	18.0%	\$0.0	N/A	\$0.2	-79.8%
20	Forteo	Eli Lilly	\$548.0	12.0%	414.0	4.0%	\$0.0	N/A	\$2.7	11.8%
21	Cimzia	UCB Pharma	\$539.3	24.0%	167.0	7.0%	\$5.1	13.0%	\$0.0	-100.0%
22	Tysabri	Biogen/Elan	\$485.6	15.0%	16.0	>100.0%	\$0.0	N/A	\$0.8	-3.1%
23	Prolia	Amgen	\$480.5	58.0%	177.0	66.0%	\$61.1	2.0%	\$0.0	-100.0%
24	Simponi	Johnson & Johnson	\$424.2	27.0%	145.0	9.0%	\$0.0	-100.0%	\$0.9	26.0%
25	Budesonide	Generic	\$406.3	6.0%	455.0	8.0%	\$0.0	N/A	\$0.0	N/A
26	Asacol HD	Actavis/Warner Chilcott	\$397.0	79.0%	695.0	68.0%	\$0.0	N/A	\$0.0	N/A
27	Prograf	Astellas	\$345.1	-17.0%	447.0	-18.0%	\$0.0	N/A	\$0.1	-29.6%
28	Actemra	Roche/Genentech	\$341.5	30.0%	22.0	21.0%	\$0.3	-90.0%	\$0.0	-97.8%
29	Actonel	Actavis/Warner Chilcott	\$329.9	-21.0%	1,623.0	-34.0%	\$0.0	N/A	\$0.0	N/A
30	Myfortic	Novartis	\$321.8	17.0%	376.0	9.0%	\$0.0	N/A	\$0.2	17.0%

Sources: Sales/TRx, IMS Healthcare; DTC media spend, Nielsen; journals, Kantar Media

List includes products FDA indicates as approved for treating rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, fibromyalgia, lupus, ankylosing spondylitis, multiple sclerosis and osteoporosis.

† >90% of sales from oncology settings

although she adds its grip will most likely begin to fade thereafter.

The emerging competitors to Humira will mostly likely focus on more palatable alternatives to Humira's injection delivery system, she says—such as drugs that can be taken orally or in more convenient dosing frequencies.

Specific treatments of this ilk include Pfizer's already approved Xeljanz (tofacitinib), which is taken orally, and Eli Lilly's Phase-III lupus drug tabalumab, Wood says. Rigel Pharmaceuticals/AstraZenica's fostamatinib, also now in Phase III for RA, will be jockeying for market share in coming years as well, she adds.

The biosimilar boom

Meanwhile, patented drugs in this sector may see increased resistance from the greater availability of biosimilars in coming years, according to Wood. Expiries on Roche/Genentech's Actemra (2015) and on Remicade (2018), for example, are set to open the floodgates for most likely cheaper alternatives.

Plus, drugmakers in the sector are also concerned by brazen manufacturers in India and China, who are developing and selling

generic knock-offs of a number of rheumatoid arthritis drugs that are still under patent, she says.

All told, the rheumatoid arthritis market is expected to become increasingly crowded in coming years, according to Wood, with a host of highly diversified therapies emerging by 2022, which will all compete for the same market.

In the psoriatic arthritis sector, Celgene is shaking up competitors with Otezla (apremilast), which won FDA approval in March. It's the first adult oral treatment for the disease approved by the FDA. And, with a PDUFA date in psoriasis coming up in September, it's expected to give competitors a real run for their money.

"Otezla offers physicians and patients a meaningful new treatment option," says Dr. Alvin Wells, director of the Rheumatology and Immunotherapy Center in Franklin, WI.

The oral phosphodiesterase-4 inhibitor is safe but it is not considered by physicians to be quite as effective as the anti-TNFs are, according to ISI Group analyst Mark Schoenebaum. "A key question for this drug is, can Celgene talk insurance companies into requiring that patients use apremilast before they move onto



CLINICAL CORNER

Research in rheumatology continues apace, including a new injection treatment found to neutralize pain in joints and late-stage results on a potential new drug for psoriasis, as well as R&D seeking to expand the indications for established products.

Scientists at the Arthritis Research Pain Center, based at Nottingham University in the UK, have found a treatment to neutralize joint pain—with apparently no side effects. The treatment targets and blocks a protein receptor in diseased joints that have been suspected to cause pain in patients with osteoarthritis.



Tim Wright

“A lot of patients who suffer with osteoarthritis are elderly and it would be better if we could treat their pain by giving them a drug, rather than putting them through a major surgical procedure like joint replacement,” says Dr. Sara Kelly, a lead researcher on the research project.

In other drug development news, according to Phase-III trials, a potentially transformative new drug for psoriasis took another step forward. Novartis says results from the trials revealed that psoriasis scabs were cleared after 12 weeks of treatment with its test drug secukinumab.

Researchers administered the treatment with a pre-filled syringe or autoinjector/pen. Tim Wright, global head of development at Novartis, says the results indicate the drug’s efficacy is “significantly superior to Enbrel, a biologic psoriasis therapy approved 10 years ago.”

AbbVie, meanwhile, continues to explore new uses of its anti-TNF juggernaut Humira. The drugmaker began testing Humira in March as a possible treatment for fingernail psoriasis. The Phase-III trial is ongoing at 32 sites worldwide and is expected to last 26 weeks.

Also filed under post-marketing research is a recent Pfizer study of Xeljanz (tofacitinib). The first of five Phase-III studies of Xeljanz indicates the drug could soon give Enbrel a run for its money. The study found that 10mg of tofacitinib taken twice daily was non-inferior, or not significantly worse than, 50mg of Enbrel taken twice weekly. Xeljanz, approved by FDA in November 2012, is the first in a class of treatments for chronic plaque psoriasis—oral janus kinase inhibitors.

And Janssen is vying to broaden its autoimmune footprint. The drugmaker reported promising results with guselkumab: 86% of patients treated with the investigational human monoclonal antibody achieved a Physicians Global Assessment score of “cleared” or “minimal” after 16 weeks, according to researchers conducting the Phase-IIb study. Guselkumab has a novel mechanism-of-action that targets the protein interleukin (IL)-23, and is being developed as a subcutaneously administered therapy for treating moderate-to-severe plaque psoriasis. “The efficacy of guselkumab in the treatment of moderate-to-severe plaque psoriasis looks promising according to these Phase 2b study results,” said Kristina Callis Duffin, MD, an assistant professor of dermatology at the University of Utah School of Medicine and a study investigator.



the injectables?” he remarked during a weekly video.

The argument for that might be that its sticker price is about 30% cheaper than that of Enbrel and Humira, he added, and perhaps could be made even cheaper through manufacturer discounts and rebates.

If Celgene can sway payers, he added, “this drug probably beats my numbers and the Street’s numbers [\$106 million this year, hitting \$1.1 billion by 2017].”

A growing sector

Market-research firm Decision Resources predicts that the psoriasis sector will experience substantial growth—up from \$5.5 billion in 2012 to \$9.2 billion in 2022, according to Kathryn Beane, an analyst at the company.

Emerging competitors also chasing those dollars include several pipeline agents, including the IL-17 inhibitors from Novartis (secukinumab), Eli Lilly (ixekizumab), Amgen/AstraZeneca/Kyowa Hakko Kirin (brodalumab) and Pfizer’s janus kinase inhibitor Xeljanz, Beane says.

Even so, Beane says dermatologists will increasingly turn to Janssen’s Stelara for their biologic-naïve patients, owing to the drug’s favorable risk/benefit profile. This is supported by years of post-marketing safety data, and will drive sales in the second half of the 2012-2022 forecast period, she says.

Beane also predicts that the emerging IL-17 inhibitors, along with Xeljanz and Merck’s IL-23 inhibitor MK-3222, will increase competition within the anti-TNF space—although there will be some initial safety concerns about the drugs.

Moreover, apremilast, the new Celgene oral poised to launch in 2014, may see use in earlier lines of therapy than the emerging biologics and Xeljanz, she says.

“Of the emerging systemic agents, the three IL-17 inhibitors—secukinumab, ixekizumab and brodalumab—as well as MK-3222, have shown the most impressive efficacy,” Beane says.

“The efficacy of ixekizumab and brodalumab in Phase-II clinical trials appears comparable to the most effective biologic for psoriasis, Janssen/Merck/Mitsubishi Tanabe’s Remicade, and Phase-III clinical trial data for secukinumab suggests impressive efficacy comparable to the two other agents in this drug class,” she adds.

“Nevertheless, reservations about these agents’ novel mechanisms of action and relatively limited safety profiles will mean that physicians will reserve these drugs initially for patients who have failed TNF-alpha inhibitors and Stelara.”

Gobbling up the competition

Besides coming up with new formulations, players in rheumatology are looking to get a leg up on the competition—and on their taxes—by gobbling up smaller drugmakers in tax-friendly countries.

Horizon Pharma, for example, recently announced plans to buy Dublin-based Vidara Therapeutics International Ltd. in a reverse merger for \$660 million. The deal will add Actimmune to its arsenal, used to treat overly dense bones, or osteopetrosis.

“The addition of Actimmune complements our commercial business model, focused on targeted promotion to primary care physicians and specialists,” says Horizon CEO Timothy Walbert.

Overall, the industry is also bracing for the entry of new generics to the market. India-based drug maker Lupin, for example, is looking to bring a cheaper, generic, injectable treatment for rheumatoid arthritis to market. ■