Breathe, breathe in the air: the anti-CCN2 antibody pamrevlumab (FG-3019) completes a successful phase II clinical trial for idiopathic pulmonary fibrosis

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Abstract

Pirfenidone and nintedanib have been approved for idiopathic pulmonary fibrosis (IPF) due to their ability to statistically slow, over a year, the rate of decline in lung forced vital capacity (FVC), neither drug has been reported to have a positive effects on high-resolution computed tomography (HRCT) of the chest, symptoms, or quality of life. Moreover, pirfenidone and nintedanib have substantial gastrointestinal tolerability issues. Overall, these data highly suggest that novel therapeutic approaches are needed. CCN2 has been shown to be a mediator of fibrosis in many preclinical models. Anti-CCN2 strategies are in clinical development for IPF. A recent study by Richeldi and colleagues described the recent Phase II clinical trial for FG-3019 in IPF, and the results were highly encouraging. This commentary contextualizes and summarizes these exciting findings.

Keywords CTGF · Connective tissue growth factor · CCN2 · FG-3019 · Pamrevlumab · Idiopathic pulmonary fibrosis · Scleroderma · Clinical trial

Key papers linking CCN2 and fibrosis in humans were published in 1995–2000 using scleroderma and lung fibrosis as a model systems (Igarashi et al. 1995, 1996; Sato et al. 2000; Allen et al. 1999). A pubmed search for “connective tissue growth factor” and fibrosis yields 2091 published manuscripts. A similar search using “CCN2” provided 676 papers. This finding completely contradicts a recent analyst’s report claiming that there is not an scientifically accepted link between CCN2 and fibrosis (<https://plainviewllc.s3.amazonaws.com/FibroGen+Presentation.pdf>).

Of course a scientific confusion, pointed out by the same analyst, arose due to the unfortunate misnaming of this protein “CTGF”. These issues have been pointed out repeatedly by this journal and its sponsoring society, and have led to the official renaming, by HUGO, of ‘CTGF’ as ‘CCN2’ (Takigawa 2018; Perbal 2018; Perbal et al. 2018). It is unfortunate that some people perpetuate this confusion by still referring to CCN2 by an archaic, incorrect and misleading name. Of course, as a matricellular protein, CCN2 is secreted

into the microenvironment to elicit its effects (Kleer 2016; Yeager and Perbal 2016). Consequently, establishing short-term in vitro assays to study these proteins is pointless; the effects must be studied in vivo (Leask 2019).

It is certainly the case that the preponderance of the scientific literature has regarded CCN2 as a marker of mechanically-activated pathological states (Schild and Trueb 2004). Since the early 1990s, FibroGen has led the way in developing an antibody that recognizes CCN2; this antibody (FG3019, pamrevlumab) may work by promoting clearance of CCN2 into the circulation (Brenner et al. 2016). Data with FG-3019 has shown that CCN2 contributes to fibrosis in a wide variety of experimental systems including in lung fibrosis and scleroderma (Lipson et al. 2012; Makino et al. 2017; Sternlicht et al. 2018). However, it has awaited the generation of genetically modified mice to definitively demonstrate that expression of endogenous CCN2 plays a direct role in experimental lung and scleroderma fibrosis (Liu et al. 2011; Parapuram et al. 2015; Makino et al. 2017) as well as skeletal muscle and the kidney (Kinashi et al. 2017; Petrosino et al. 2019). CCN2 appears to be essential for activation of fibroblasts to myofibroblasts, the critical effector cells of fibrosis, likely via progenitor cell intermediates (Tsang et al. 2019). Collectively, these data, again, contradict the analyst’s aforementioned report that CCN2 has no role in fibrosis.

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A particularly exciting paper, recently published in *Lancet Respiratory Medicine* (Richeldi et al. 2019), described the recently successful Phase II clinical trial, PRAISE, which was a randomised, double-blind, placebo-controlled trial of the anti-CCN2 antibody FG-3019 (pamrevlumab) in idiopathic pulmonary fibrosis (IPF) ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01890265), NCT01890265.) PRAISE was conducted at 39 medical centres in seven countries. Patients, 40–80 years of age, were within 5 years of initial diagnosis of IPF. Patients received intravenous pamrevlumab or matching placebo over 48 weeks. Significantly, and in contrast to other Phase II trials for IPF, a variety of approaches were used to examine efficacy and safety, including not only assessing forced vital capacity (FVC), but also using high-resolution computed tomography (HRCT) scans and a self-administered health-related quality of life questionnaire.

FG-3019 significantly reduced the decrease in FVC and slowed disease progression. The quantitative HRCT scores were significantly lower in the pamrevlumab group. Quality-of-life measure, at week 48, showed a non-significant improvement with pamrevlulab.. No safety concerns were identified.

In conclusion, pamrevlumab may be a key therapeutic option for IPF patients; this concept pulmonary will be tested further in a phase III trial (ZEPHYRUS; NCT03955146).

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