

D#17

Viewing FOP Through Rosi-Colored Glasses

(An Editorial)

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Background on FOP

Fibrodysplasia ossificans progressiva (FOP) is one of the most disabling conditions known to mankind. The childhood victims of this rare musculoskeletal sabotage appear normal at birth except for characteristic malformations of the great toes.^{1,2} That is the last time, however, that things appear relatively normal for the world's approximately 800 known individuals with this condition. Soon thereafter, children with FOP succumb to progressive waves of inflammation-induced ectopic skeletogenesis that transform the body's soft connective tissues into an armament-like encasement of bone, in effect, a second skeleton.^{1,2} Massive and rapidly-appearing soft-tissue swellings (flare-ups) are often the first sign of the metamorphosis.³ Ribbons, sheets, and plates of heterotopic bone replace the body's soft connective tissues, span the joints, lock them in place, and relegate its victims to permanent and lifelong immobility. Any attempt to remove this heterotopic bone leads to additional episodes of explosive soft tissue swelling and subsequent new bone growth.¹⁻³

Historical Context

Nearly a century ago, Jules Rosenstirn of San Francisco wrote: "One does not wonder that a disease, so baffling in its course from the first causes to its ultimate state, should invite the speculative as well as the patiently investigating observer to lift the obscuring veil and solve this embarrassing puzzle."⁴ An embarrassing puzzle it remained for nearly another century until early 2006 when the FOP gene was discovered with a liberating wave of hope.⁵

The discovery of the FOP gene, coupled with the extraordinary specificity of the causative mutation in a highly conserved bone morphogenetic protein (BMP) receptor, immediately predicted the discovery of molecules to block it.⁶⁻¹⁰ “With so much being discovered about how the BMPs act,” said Brigid Hogan, a prominent developmental geneticist, nearly a decade earlier in response to emerging discoveries in FOP, “it might be possible to develop drugs that would block some part of the BMP pathway, and therefore prevent the progression of what is a horrible nightmare disease.”^{11,12} Presently, work is proceeding diligently in that direction.

A Recent Case Report: Rosiglitazone & FOP

A recent case report by Gatti et al from the University of Verona (Verona, Italy), published in the **Journal of Bone and Mineral Research** (Epub ahead of print; Nov, 2009) approaches the problem from a different perspective.¹³ The case report claims that rosiglitazone, an anti-inflammatory and anti-diabetic agent that alters the fate of marrow stromal cells, “is associated with major clinical improvements in a patient with fibrodysplasia ossificans progressiva (FOP).”¹³

Here, we will briefly summarize the case report and critically evaluate its conclusions. Finally, we will summarize our conclusions and propose recommendations to address emerging concerns.

In the case report, Gatti et al describe “a 48 year-old woman with severe FOP characterized by continuous flares that she was partially controlling only with high

prednisone doses. She was given rosiglitazone (initially 4 mgs, and then 8 mgs daily) for 14 months. No new flares were observed during rosiglitazone therapy, as compared to the five episodes observed during the previous year while on 20-25 mgs of prednisone daily. The steroid dose was progressively lowered to 5 mgs daily, the skin became softer and the articular mobility impressively improved,” according to the authors. The authors conclude that “rosiglitazone therapy, possibly in association with small doses of prednisone, is associated with important clinical improvements in patients with FOP.”¹³ First, we will address, “What is rosiglitazone?” and then evaluate safety concerns about the use of rosiglitazone in FOP.

What is Rosiglitazone?

Rosiglitazone is an anti-diabetic drug, useful for the treatment of type 2 diabetes.^{14,15} In addition to its effect on insulin-resistance, it appears to have a potent anti-inflammatory effect,^{16,17} as well as an adverse effect on the normal skeleton.^{18,19} The most likely mechanism contributing to the damaging skeletal effects of rosiglitazone include activation of the nuclear receptor PPAR- γ , which at least in the bone marrow, triggers the preferential differentiation of marrow stromal cells into adipocytes (fat cells) rather than osteoblasts (bone cells).^{20,21} The authors postulate that these adverse skeletal effects might be exploited therapeutically for diseases characterized by excessive bone formation, such as in FOP.¹³

Safety Concerns About Rosiglitazone

In 2005, safety concerns emerged about the use of rosiglitazone. Rosiglitazone was noted to cause macular edema and partial blindness.²² While blindness is also a possible effect of diabetes (which rosiglitazone is intended to treat), several articles have documented occurrences of macular edema and recommended the discontinuation of rosiglitazone at the first sign of vision problems.^{15,22}

Later, data from clinical trials warned of a greater incidence of fractures in diabetics given rosiglitazone compared to those given other oral anti-diabetic medications.²³⁻²⁶

In May 2007, a meta-analysis reported that rosiglitazone was associated with a significantly increased risk of heart attack and death from all cardiovascular causes.²⁷⁻²⁸

The US Food and Drug Administration (FDA) issued an alert. An advisory committee of the FDA concluded that the use of rosiglitazone was associated with a greater risk of heart attacks than a placebo.²⁹

In summary, there are major safety concerns about the chronic use of rosiglitazone:

1. Rosiglitazone use has considerable adverse cardiovascular side effects including an increased risk of heart attacks and death from all cardiovascular causes.^{15,27-29}

2. Rosiglitazone causes severe osteoporosis and decreased strength in the normotopic skeleton that is reminiscent of aged bone.^{18,19} Pathologic fractures of the long bones occur with chronic rosiglitazone use.²³⁻²⁶
3. Rosiglitazone causes ophthalmologic side-effects, specifically macular edema and blindness.^{15,22}
4. Rosiglitazone is not approved for use in children.

FOP & Rosiglitazone: The Interpretation of Data

Next, we will address concerns about the interpretation of data in the case report by Gatti et al. Specifically:

1. The authors conclude that “rosiglitazone therapy is associated with important clinical improvements in patients with FOP.” The data do not support this claim. First, the patient is a 48 year-old woman and already severely affected with FOP. It is likely that there were few, if any, remaining soft connective tissues to become involved. Second, rosiglitazone was used anecdotally in a single patient, not in multiple patients, as implied. Third, and most importantly, there were no controls employed to help determine whether rosiglitazone was effective. Specifically, the rosiglitazone was not discontinued to see if the clinical course was altered and then re-started to assess any further clinical changes. Such critical controls, which

would have minimally satisfied Koch's postulates for possible therapeutic effects, were not employed, and are essential in order to draw valid conclusions from anecdotal observations.

2. As stated in the **“Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations”** by the International Clinical Consortium on FOP: “Flare-ups of FOP are sporadic and unpredictable, and there is great individual variability in the rate of disease progression. Several large studies on the natural history of FOP have confirmed that it is impossible to predict the occurrence, duration, or severity of an FOP flare-up.”³⁰ Thus, the clinical course of a single individual can not be used to assess therapeutic efficacy.

3. The rarity of FOP and the unpredictable nature of the condition make it extremely difficult to assess any therapeutic intervention, a fact recognized as early as 1918 by Jules Rosenstirn, who noted:

“The disease was attacked with all sorts of remedies and alternatives for faulty metabolism; every one of them with more or less marked success observed solely by its original author, but pronounced a complete failure by every other follower. In many cases, the symptoms of the disease disappear often spontaneously, so the therapeutic effect (of any treatment) should not be unreservedly endorsed.”¹⁴ In other words, without proper controls, it is easy to see what you want to see.

4. Exacerbations and remissions are common in FOP and often occur spontaneously. Almost every adult with FOP has experienced a remission while taking a medication that was later proven useless.³⁰ Historically, the treatment regimen described in the case report was no better than placebo.

5. It is not possible from the data presented, to separate the effects, if any, of rosiglitazone from those of chronic prednisone use. If rosiglitazone has therapeutic anti-inflammatory activity in FOP, it is most likely through its in effect on suppressing monocyte and tissue macrophage function.¹⁷ However, the anecdotal use of rosiglitazone in the described patient can not be isolated from the effect of prednisone. Although high dose, long-term prednisone use is not recommended for the treatment of FOP, its use in animal models has shown to be effective in decreasing the intensity of FOP-like flare-ups.³⁰

6. In FOP, heterotopic bone forms through a cartilage intermediate.² Rosiglitazone is not known to disrupt cartilage formation. It is possible that its modest anti-inflammatory effect could have led to the quiescence of flare-ups noted in this patient. Alternatively, the attributed effect might have been a spontaneous occurrence unrelated to the medication, or possibly a delayed effect of the chronic high dose prednisone use.³⁰

7. Rosiglitazone affects stromal cells of bone marrow origin. However, it is not clear what effect, if any, those cells have on lesions in skeletal muscle and other connective tissues in patients with FOP.^{20,21}

Recommendations & Future Directions

Despite the substantial morbidity and mortality associated with chronic rosiglitazone use and the numerous biases inherent in the case report, the observation in this single patient is sufficiently interesting to prompt further investigation in emerging animal models of FOP and FOP-like heterotopic ossification.^{31,32} Such investigation would not have been possible even several short years ago before the discovery of the FOP gene and the use of that knowledge to create genetically-engineered mice with the identical mutation.^{5,32} Such studies are now possible.³³ Ultimately, these studies must separate the postulated and presently unsubstantiated effects of rosiglitazone in FOP from the known effects of prednisone. *In vivo* testing of rosiglitazone in animal models of FOP is necessary to determine if there may be a physiological basis for a limited use in FOP, considering its safety profile.

FOP is a catastrophic disease with unimaginable human suffering. Affected individuals and their families are vulnerable to hype, and are suspicious of inflated claims. In our opinion, rosiglitazone should not be used in any FOP patient without Investigational Review Board approval and the most detailed warnings about morbidity and mortality. At the present time, we would favor *in vivo* studies in emerging animal models of FOP. Extreme caution is necessary until the results of animal testing are completed and it can

be determined whether or not there is a physiological basis for rosiglitazone use in treating or preventing FOP flare-ups.

In summary, the key questions remain:

1. Does rosiglitazone reduce or prevent FOP flare-ups?
2. If so, is rosiglitazone safe enough to warrant its chronic use in patients with FOP?"

The simple answer to both questions is “perhaps, but we do not know.” It is prudent to get real answers before viewing FOP through Rosi-colored glasses.

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