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Updated statement regarding off label medications for the management of FOP, from the International Clinical Council (ICC) on FOP

This statement updates the recommendations from the ICC to include several new publications, and brings attention to an important potentially severe medication interaction with palovarotene.

The International Clinical Council (ICC) on FOP clinicians are aware of several recent publications describing the off-label use of potent medications for managing inflammation in FOP. These potential treatments include the use of anakinra (1), canakinumab (1; 2), tofacitinib (3), and imatinib (4; 5). These reports appear to show some benefits, particularly with managing FOP flares and flare pain.

In addition, there are recent reports of medications such as minocycline (6), momelotinib (7), and pacritinib (8) that have activity in animal models of FOP or that may directly target ACVR1 activity. There are no clinical data regarding the risks or benefits of these therapies for managing patients with FOP.

These off-label and investigational medications have very limited data. We have no or limited data on:

1) whether the benefit is only for reducing flares (which is what has been reported for all of these medications);

2) whether there is any benefit for function or reducing heterotopic ossification in FOP;

3) the long-term safety of these medications in patients with FOP; and

4) what happens when a patient stops the medication.

We also have very little or no systematic data for the safety of these medications in children with FOP, even though many of these medications have been used in children with non-FOP conditions.

These preliminary studies support the need for larger, well controlled, human clinical trials to determine the safety and efficacy of these medications in FOP.

Until those studies are completed, the ICC recommends considering these medications only for situations where all three minimal key criteria are met:

1. FOP flares are considered severe and intractable, or where there is unusually severe or rapid progression of the disease, and
2. Once standard of care therapies (ICCFOP.org) have been exhausted, and
3. The clinical team feels that the medications could be used safely (i.e. no other contra-indications, no underlying problems with infection, no immunocompromised situations, no medication interactions, etc.) and according to the age at which these drugs may have been authorized.

The ICC brings particular attention to medications that have potentially severe interactions with palovarotene. This includes all tetracycline-like drugs such as minocycline or doxycycline (see FDA label) (9). Taking these medications with palovarotene or other retinoids can significantly increase the risk of intracranial hypertension (also known as pseudotumor cerebri), a potentially dangerous condition of high pressure inside the skull that can damage the brain and nervous system (10). It is important for all patients considering new medications to discuss their options with their medical team.

Due to the risk profiles of all these medications, the ICC does NOT recommend the use of off-label medications as a preventive.

If you wish to consider these medications for you or your child, please discuss the pros and cons in detail with your doctors and FOP clinicians. ***Medication interactions and individual risks vary and can be severe.*** These risks must be discussed at the individual patient level***.***

Social media claims of safety or efficacy are not the same as an open medical discussion of potential risks and benefits. The ICC believes in individual choice. Whether someone takes a potential therapy, or feels that a therapy works, is an individual judgment that must be made with all available risks and benefits clearly presented.

The ICC also recommends review of active clinical trials before making decisions regarding off-label use of these medications. Taking any of these off-label or investigational medications may disqualify you or your child from participation in formal clinical trials. In addition, clinical trials are monitored closely for safety and efficacy, and information from those clinical trials can help the FOP community advance different therapeutic options and support future drug approvals. Information from off-label use of a medication outside of a clinical study is not sufficient for drug approval.

If you choose to use these medications, or any other medications that are not considered standard-of-care for patients with FOP, it should be done with close monitoring in collaboration with your FOP clinical team. If you are in a clinical trial, you must discuss any potential changes to your therapy before starting a new medication. Off-label medications are often not allowed during your participation in a clinical trial.

The ICC strongly recommends following the most up-to-date version of the consensus Treatment Guidelines, available on the ICCFOP.org webpage.

About the ICC: The International Clinical Council on FOP (The ICC) is an autonomous and independent group of 21 internationally recognized physicians who are clinical experts in FOP from 14 nations (Argentina, Australia, Brazil, China, France, Germany, Italy, Japan, Netherlands, South Korea, United Kingdom, Mexico, India, and United States) and six

continents (Africa, Asia, Australia, Europe, North America and South America). The ICC was established to coordinate and consolidate a global voice for the best practices for clinical care and clinical research for people who live with FOP. The ICC publishes the FOP Clinical Treatment Guidelines, which is used internationally to guide the management of patients with FOP (ICCFOP.org) (11). The ICC also has published key recommendations for clinical trials testing potential therapies for FOP (12).

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