Musculoskeletal Tumor Society Information Statement

Pexidartinib (Turalio®)

Novel Practice Assessment

In these occasional Novel Practice Assessments, the MSTS Guidelines and Evidence Based Medicine committee will assess the evidence underlying novel diagnostics or therapeutics entering musculoskeletal oncology clinical practice. The goal is assist MSTS members make more informed decisions for their patients. As evidence is expected to change rapidly, articles will be rewritten or removed after one year.

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Summary

Pros

1. Non-surgical, non-radiation option for patients with tenosynovial giant cell tumor that have failed surgical treatment or are not surgical candidates

Cons

1. Some trial patients experienced severe hepatotoxicity
2. Need to be enrolled in manufacturer's Risk Evaluation and Mitigation Strategy program to prescribe
3. Cost
4. Unclear how long to continue therapy or if it should be done in conjunction with surgery

Background

Tenosynovial giant cell tumor (TSGCT, "pigmented villonodular synovitis") is a synovial neoplasm mixed with inflammatory response. Only a minority of the neoplastic cells express CSF-1 as a result of genomic aberrations on chromosome 1p13. However, this overexpression recruits numerous monocytes, macrophages, and other inflammatory cells to the milleu.[1]

What is new ?

Pexidartinib (Turalio®) is a novel small molecule immune checkpoint tyrosine kinase inhibitor with selective activity against the CSF-1 receptor (CSF-1R).

Methods

A search of PubMed online database and clinicaltrials.gov was performed on 12/4/2022. Search terms included "ENLIVEN," "pexidartinib," "Turalio," "tenosynovial giant cell tumor," "pigmented villonodular synovitis," "CSF-1 inhibitor," "CSF-1R inhibitor," "CSF-1 receptor inhibitor," "colony stimulating factor 1 inhibitor," and "colony stimulating factor 1 receptor inhibitor." Limits were placed to exclude non-English manuscripts and case reports.

A total of 6,420 citations were identified. After exclusion for duplicates, non-English studies, case reports, treatment for diseases other than TSGCT, and narrative review articles, 5 total citations were included (references #2-6 below).

What is the evidence in favor?

The ENLIVEN Clinical trial was a Phase III, open label, double blind, placebo controlled, clinical trial investigating the safety and efficacy of pexidartinib (Turalio®), a targeted CSF-1R tyrosine kinase inhibitor, for the treatment of symptomatic, refractory or recurrent, and unresectable diffuse tenosynovial giant cell tumor (D-TSGCT).[2] Funding and study design for the ENLIVEN trial was provided by Daiichi-Sankyo, makers of pexidartinib. However, an independent data monitoring committee was responsible for patient safety and overseeing the study.

A previous Phase I study in 23 patients with recurrent or inoperable D-TSGCT resulted in a 52% response rate by RECIST.[3] Final enrollment in ENLIVEN included 120 patients (61 receiving pexidartinib and 59 receiving placebo). There were no significant demographic differences between groups, and the knee was the most common anatomic site. Nine patients receiving pexidartinib and 11 in the placebo group withdrew from the study due to adverse events.

Overall response rate by RECIST was 39% vs. 0% in the pexidartinib vs. placebo groups, and all responses were maintained out to 6 months of follow-up. Range of motion, PROMIS functional outcome scores, stiffness, and pain were all also improved in the pexidartinib group over placebo and correlated with RECIST response. However, 30 patients crossed over from the placebo to pexidartinib group. Additionally, those allocated to the placebo group were allowed to receive the drug after 6 months.[2]

Continued follow-up of patients in the ENLIVEN trial over several years have demonstrated lasting and improved response rates compared to those seen during the active trial.[4] Additionally, post-hoc analysis of the cohort revealed a modest benefit to pain relief, just exceeding the MCID.[5]

The ENLIVEN clinical trial involved daily dosing from 800-1200 mg following a 2-week increased loading dose up to 1200 mg.[2] Because of the hepatotoxicity seen in the trial at higher doses along with subsequent noninferiority studies, current FDA-approved treatment recommendations for pexidartinib are an oral 400 mg tablet, twice daily with no loading dose (800 mg/d), or 400 mg in the morning and 200 mg in the evening (600 mg/d) in patients with renal impairment.[4]

What is the evidence against?

Grade 3 or 4 adverse events (AEs) occurred in 27 (44%) and 7 (12%) patients receiving pexidartinib or placebo, respectively. The AEs that occurred more frequently in the pexidartinib included skin and hair pigment changes (61% vs. 3%) and elevations in ALT, AST, and ALP (7-

10% vs. 0%). Seven patients discontinued pexidartinib due to mixed and cholestatic liver toxicity. Most of the hepatotoxicity was reversible within 1-2 months of stopping pexidartinib. However, the 2 most concerning cases were a case needing liver transplant (pexidartinib 1200 mg/d combined with paclitaxel) and a case associated with death (pexidartinib 1000 mg/d mono therapy in a patient with advanced, loco-regionally progressing mucosal melanoma).[2] In these cases, serious hepatotoxicity emerged within the first 2 months of treatment that warrants aggressive LFT monitoring during the first 8 weeks of administration. Pexidartinib should be avoided in patients with preexisting liver or biliary tract diseases and in patients with elevated bilirubin or transaminases at baseline.[4]

Findings from animal studies suggest pexidartinib may impair both male and female fertility, and is a potential teratogen to a developing fetus. Therefore, patients should be counseled appropriately and in women of child-bearing age, pregnancy status must be verified with adequate contraception used during the course of treatment and 1 week after the final dose. Similarly, lactating women should not breastfeed during the course of treatment and 1 week after the final dose. The wholesale acquisition cost for a 28-day supply of pexidartinib is US$18,480 for the 800-mg daily dose. Copay programs and payment assistant programs are available for eligible patients.[6] Because of the black box warning regarding the risk of serious and potentially fatal liver injury, it is prescribed and dispensed solely via a manufacturer-supported Risk Evaluation and Mitigation Strategy safety program.[7]

Future Directions

Questions that remain to be answered with future research are precise indications for the use pexidartinib, pexidartinib as monotherapy vs. adjuvant to surgery, optimal dosing, optimal duration of treatment, and safety and efficacy in children. Other small molecule CSF-1R inhibitors currently being developed or investigated include ARRY-382 (Array BioPharma), PLX7486 (Plexxikon), BLZ945 (Novartis), and JNJ-40346527 (Johnson& Johnson). Current anti-CSF-1R mAbs include emactuzumab (Roche), AMG820 (Amgen), IMC-CS4 (also referred to as LY3022855; Eli Lilly), cabiralizumab (Five Prime Therapeutics), MCS110 (Novartis; CSF-1), PD-0360324 (Pfizer, CSF-1),[8] and the intraarticular CSF1R inhibitor, AMB-05X (AmMax Bio, Inc.).[9]

Sources:

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