Aflibercept

ACG: A-0680 (AC)
Link to Codes

MCG Health
Ambulatory Care
27th Edition

Clinical Indications

- Aflibercept may be indicated when **ALL** of the following are present(1)(2):
  - Age 18 years or older
  - Clinical diagnosis of **1 or more** of the following:
    - Diabetic macular edema[A](13)(14)(15)(16)(17)(18)N
    - Diabetic retinopathy[B](30)(31)N
    - Macular edema following central or branch retinal vein occlusion[C](34)(35)(36)(37)N
    - Metastatic colorectal cancer[D] with progression of disease on initial therapy(46)(47)(48)N
    - Neovascular (wet, or exudative) age-related macular degeneration[E](14)(37)(55)(56)(57)N
  - No active intraocular inflammation(67)
  - No concurrent ocular or periocular infection(67)

Evidence Summary

Background

Aflibercept acts as a decoy receptor that binds vascular endothelial growth factor, which inhibits its role in promoting neovascularization and vascular permeability.(1)(3)(4) **(EG 2)**

Criteria

For diabetic macular edema, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Meta-analyses and systematic reviews have demonstrated that all vascular endothelial growth factor inhibitors appear to have some activity against diabetic macular edema,(19) with some clinical trial evidence suggesting that aflibercept may improve best-corrected visual acuity (measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters) significantly compared with bevacizumab, without a statistically significant difference compared with ranibizumab.(20) **(EG 1)** A multicenter randomized double-masked study of 221 patients with diabetic macular edema reported significant improvement with aflibercept in mean best-corrected visual acuity after 24 weeks and 52 weeks.(21)(22) **(EG 1)** A randomized study of 872 eyes of patients with central involvement of diabetic macular edema found that intravitreal administration of aflibercept, as compared with laser photocoagulation, produced significantly greater improvement in both visual acuity and central retinal thickness after 52 weeks.(23) **(EG 1)** Follow-up studies showed that incremental visual acuity benefits were maintained at 100 weeks to 148 weeks.(24)(25) **(EG 1)** A randomized study of 660 adults with diabetic macular edema who received either intravitreal aflibercept, ranibizumab, or bevacizumab found that, after 1 year, visual acuity improvement was comparable among all 3 drugs in those with mild initial visual acuity loss; however, for those with worse initial levels of visual acuity, aflibercept was more effective at improving vision.(26) **(EG 1)** A follow-up study for up to 2 years found that all 3 groups showed continuing improvement in visual acuity, with similar improvement across all 3 drugs in eyes with better baseline acuity. However, among eyes with poorer baseline acuity, aflibercept had significantly better acuity improvement after 2 years as compared with bevacizumab.(27)(28) **(EG 1)** A secondary analysis also found, in eyes with proliferative diabetic retinopathy at baseline, that aflibercept therapy for diabetic macular edema was associated with a higher rate of diabetic retinopathy improvement compared with bevacizumab at both 1-year (75.9% vs 31.4%, respectively) and 2-year (70.4% vs 30.3%, respectively) follow-up; bevacizumab was also associated with a higher rate of improvement compared with ranibizumab at both 1-year (75.9% vs 55.2%, respectively) and 2-year (70.4% vs 37.5%, respectively) follow-up.(29) **(EG 1)** Review articles indicate that aflibercept use was found to be associated with improvement in the severity of diabetic retinopathy in patients with diabetic macular edema as a secondary outcome during clinical trials.(17)(18) **(EG 2)**

For diabetic retinopathy, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A multicenter phase III randomized trial of 402 adult patients with severe nonproliferative diabetic retinopathy without macular edema compared treatment with either intravitreal aflibercept (at 1 of 2 dosing regimens) or sham injection and found, at 52-week and 100-week follow-up, that aflibercept at either dose was associated with more patients achieving a 2-step or greater improvement in Diabetic Retinopathy Severity Scores (DRSS), fewer vision-threatening complications, and a lower rate of development of center-involved diabetic macular edema compared with sham injection.(32) **(EG 1)** A phase II noninferiority trial of 221 patients with active proliferative diabetic retinopathy compared treatment with aflibercept or panretinal laser photocoagulation and found, at 52-week follow-up, that aflibercept was noninferior to laser photocoagulation for best-corrected visual acuity change from baseline.(30) **(EG 1)** A review article notes that patients with diabetic retinopathy who are treated with vascular endothelial growth factor inhibitors may have less visual field loss, less development of diabetic macular edema, and less need for vitrectomy surgery compared with patients treated with panretinal photocoagulation.(31) **(EG 2)**

For macular edema following central or branch retinal vein occlusion, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Meta-analyses and systematic reviews have confirmed the efficacy and safety of vascular endothelial growth factor inhibitors for treatment of central and branch retinal vein occlusions for up to 26 to 52 weeks.(38)(39)(40)(41) **(EG 1)** The gains in visual acuity with aflibercept were maintained at 52-week and 76-week follow-up.(42) **(EG 1)** A randomized noninferiority trial of 463 patients with macular edema due to central retinal vein occlusion compared treatment with ranibizumab, aflibercept, or bevacizumab and found, at 100-week follow-up, mean gains in best-corrected visual acuity letter scores of 12.5, 15.1, and 9.8 in patients treated with ranibizumab, aflibercept, and bevacizumab, respectively. The authors found that aflibercept was noninferior compared with ranibizumab; however, bevacizumab was not noninferior compared with ranibizumab.(43) **(EG 1)** Specialty society guidelines state that aflibercept is an effective treatment for macular edema due to retinal vein occlusion.(44)(45) **(EG 2)**

For metastatic colorectal cancer with progression of disease on initial therapy, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A randomized phase III trial of 1226 patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen reported that the addition of aflibercept to standard fluoropyrimidine-based chemotherapy resulted in an improved mean overall survival of 13.5 months, as compared with 12.1 months in the group receiving standard chemotherapy.(49) **(EG 1)** Longer-term follow-up analysis of safety and efficacy of this phase III study indicated the following probabilities of survival for those receiving aflibercept vs placebo: 38.5% vs 30.9% at 18 months, 28% vs 18.7% at 24 months, and 22.3% vs 12% at 30 months; the majority of the most severe adverse events occurred within earlier cycles of treatment.(50) **(EG 1)** A post hoc analysis of this study suggested that inclusion of some patients who had rapidly relapsed within 6 months of oxaliplatin-containing adjuvant chemotherapy may have resulted in understating the treatment benefit of aflibercept in patients who did not belong to this poor prognosis subgroup.(51) **(EG 2)** A technology assessment stated that the impact of aflibercept on overall survival of patients with metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy was statistically significant but clinically small.(52) **(EG 1)** A meta-analysis of the use of aflibercept for treating various solid tumors found a significantly higher rate of fatal drug-related adverse events in treated patients as compared with controls, with an overall incidence of fatal events of 5.1%.(9) **(EG 1)** A meta-analysis stated that the incidence of severe infections in patients with solid tumors who were treated with aflibercept was 7.3%, and the mortality rate was 2.2%.(53) **(EG 1)** Expert consensus guidelines state that aflibercept, when given in conjunction with other chemotherapeutics (such as irinotecan or the folinic acid, fluorouracil, and irinotecan (FOLFIRI) regimen), may be appropriate for patients with metastatic colorectal cancer who have progressed on initial therapy. Aflibercept plus FOLFIRI is only appropriate for those patients who have not yet been exposed to any other treatment regimen containing FOLFIRI.(46)(47) **(EG 2)**

For neovascular age-related macular degeneration, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A meta-analysis and systematic review identified 2 randomized trials with a total of 2457 patients with neovascular age-related macular degeneration who received either intravitreal aflibercept or ranibizumab and found that patients achieved comparable improvement in visual acuity with either drug up to 1 year after initiation of treatment.(58) **(EG 1)** However, other authors have found that intraocular pressure is higher in patients who receive ranibizumab as compared with aflibercept.(59) **(EG 1)** Follow-up studies of patients treated with either ranibizumab or aflibercept for neovascular age-related macular degeneration indicate continued comparable effectiveness in improving visual acuity and preventing further vision loss for up to 96 weeks.(60)(61) **(EG 1)** A randomized trial of 278 patients with neovascular age-related macular degeneration compared treatment with intravitreal aflibercept or ranibizumab and found, at 24-month follow-up, no difference in development or growth of macular atrophy or change in best-corrected visual acuity between the groups.(62) **(EG 1)** A randomized trial of 127 patients with intermediate nonexudative age-related macular degeneration compared prophylactic treatment with either intravitreal aflibercept or sham injection and found, at 24-month follow-up, no difference in rates of conversion to exudative macular degeneration between groups.(63) **(EG 1)** Critical reviews of studies have found some evidence that switching from either ranibizumab or bevacizumab to aflibercept in refractory patients may further improve visual acuity outcomes. However, the authors caution that additional confirmatory randomized controlled trials are necessary.(64)(65) **(EG 2)** A specialty society guideline recommends aflibercept as a management option for patients with neovascular age-related macular degeneration.(66) **(EG 2)**

Inconclusive or Non-Supportive Evidence

For non-small cell lung cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A multicenter double-blind placebo-controlled trial of 913 patients with advanced or metastatic nonsquamous non-small cell lung cancer reported that the addition of aflibercept to standard docetaxel therapy did not improve overall survival and was associated with increased toxicities.(5)(6) **(EG 1)** Several cases of reversible posterior

leukoencephalopathy syndrome have been observed in a phase II study of non-small cell lung cancer patients receiving a combination of aflibercept, pemetrexed, and cisplatin.(7) **(EG 2)**

For ovarian cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized phase II study of 84 patients with platinum-resistant advanced ovarian cancer found that while the drug was well tolerated, the desired efficacy endpoints were not achieved.(8) **(EG 1)** A meta-analysis of the use of aflibercept for treating various solid tumors found a significantly higher rate of fatal drug-related adverse events in treated patients as compared with controls, with an overall incidence of fatal events of 5.1%.(9) **(EG 1)**

For pancreatic cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A phase III randomized study assigned 546 patients with metastatic pancreatic cancer to gemcitabine with or without aflibercept. The study was terminated when it was noted that the addition of aflibercept failed to significantly improve overall survival.(10) **(EG 1)** A meta-analysis of the use of aflibercept for treating various solid tumors found a significantly higher rate of fatal drug-related adverse events in treated patients as compared with controls, with an overall incidence of fatal events of 5.1%.(9) **(EG 1)**

For prostate cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A phase III randomized study of 1224 patients with metastatic castration-resistant prostate cancer found that adding aflibercept to docetaxel and prednisone as first-line therapy resulted in no improvement in overall survival and incurred additional adverse effects. The authors indicated that docetaxel plus prednisone remains the standard treatment.(11) **(EG 1)** A meta-analysis of the use of aflibercept for treating various solid tumors found a significantly higher rate of fatal drug-related adverse events in treated patients as compared with controls, with an overall incidence of fatal events of 5.1%.(9) **(EG 1)**

For retinopathy of prematurity (ROP), evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 6 studies (all cohort studies or case series) including 218 eyes in patients with ROP evaluated intravitreal aflibercept injection at half the adult dose as initial therapy for prethreshold type 1 ROP, threshold ROP, and aggressive posterior ROP and found that aflibercept therapy resulted in a 97% average regression rate and a 16% average recurrence rate. However, the authors noted that randomized controlled trials are needed to compare outcomes for the various anti-vascular endothelial growth factor agents and evaluate safety in this population.(12) **(EG 1)**

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Footnotes

[A] For diabetic macular edema, aflibercept is administered by intravitreal injection every 4 weeks for the first 5 injections, and then continued by intravitreal injection every 4 to 8 weeks. Patients should be monitored for postinjection complications, including increased intraocular pressure, endophthalmitis, and retinal detachment.(1) [A in Context Link 1]

[B] For diabetic retinopathy, aflibercept is administered by intravitreal injection every 4 weeks for the first 5 injections, and then continued by intravitreal injection every 4 to 8 weeks. Patients should be monitored for postinjection complications, including increased intraocular pressure, endophthalmitis, and retinal detachment.(1) [B in Context Link 1]

[C] For macular edema following central or branch retinal vein occlusion, aflibercept is administered by intravitreal injection every 4 weeks.(1) Patients should be monitored for postinjection complications, including increased intraocular pressure, endophthalmitis, and retinal detachment.(1)(33) [C in Context Link 1]

[D] For metastatic colorectal cancer, aflibercept is administered by intravenous infusion over 1 hour every 2 weeks.(2) [D in Context Link 1]

[E] For neovascular (wet, or exudative) age-related macular degeneration, aflibercept is administered by intravitreal injection every 4 weeks for the first 3 months of treatment, then continued by intravitreal injection every 4 to 8 weeks(1); after 1 year of therapy, the dosing frequency may be extended by 2 weeks in eyes with inactive disease until a dosing frequency of every 12 weeks is reached, assuming the disease remains inactive.(54) Patients should be monitored for postinjection complications, including increased intraocular pressure, endophthalmitis, and retinal detachment.(1) [E in Context Link 1]

Codes

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