NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of daratumumab within its marketing authorisation in combination for newly diagnosed systemic amyloid light-chain amyloidosis.

Background

Amyloid light-chain (AL) amyloidosis is caused by plasma cells in the bone marrow producing abnormal forms of light-chain proteins[1]. These can form amyloid deposits, which clump together into amyloid fibrils and build up as deposits in tissues and organs, gradually stopping them from functioning normally[1]. AL amyloidosis usually affects multiple organs, but one of them is often more affected than others[2]. Any organ except the brain can be involved, including the heart, kidneys, stomach, intestines, liver, nerves or skin[2]. About 70% of patients have heart involvement and 68% have multiple organ involvement[3]. Multiple organ damage and heart dysfunction have a negative impact on survival[3]. AL amyloidosis can cause general symptoms such as weight loss, fatigue, weakness, loss of appetite and bruising[2].

About 500 to 600 cases of AL amyloidosis are diagnosed each year in the UK[1]. The 1-year mortality rate is estimated to be around 40%[4].

There is no standard treatment for AL amyloidosis. Current treatment options are based on anti-myeloma therapy, including immunomodulatory drugs (such as thalidomide) and proteasome inhibitors (such as bortezomib). A person's age, comorbidities, the extent of organ involvement and personal treatment preferences are taken into account when considering treatment options. Autologous stem cell transplant with high dose melphalan may be an option for some people aged up to 65 to 70 years. A palliative treatment approach may be appropriate for people with worse disease[5]. Best supportive care is dependent on individuals' organ involvement but includes renal and/or heart failure therapy.

The technology

Daratumumab (Darzalex, Janssen) is a monoclonal antibody that binds to the cell-surface protein CD38, inhibiting the growth of these cells. CD38 is expressed on the plasma cells that produce the abnormal light-chain proteins, so inhibiting the growth of these cells may reduce the production of these proteins. It is available as an intravenous infusion or a subcutaneous formulation.

Daratumumab does not currently have a marketing authorisation in the UK for adults with newly diagnosed systemic amyloid light-chain amyloidosis. If has been studied in a clinical trial with cyclophosphamide, bortezomib and dexamethasone, compared with cyclophosphamide, bortezomib and dexamethasone alone, in adults with newly diagnosed systemic AL amyloidosis.

Intervention(s)	Daratumumab with cyclophosphamide, bortezomib and dexamethasone
Population(s)	Adults with newly diagnosed systemic amyloid light-chain amyloidosis
Comparators	Established clinical management without daratumumab. This may include: • Bortezomib with dexamethasone, an alkylating treatment and/or immunomodulatory drugs • Lenalidomide with dexamethasone • Melphalan and dexamethasone • Autologous stem cell transplant with high dose melphalan • Best supportive care (None of the comparators listed have a marketing authorisation in the UK for this indication)
Outcomes	The outcome measures to be considered include: • haematologic response rates • organ response rates • progression-free survival • major organ deterioration progression-free survival • overall survival • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.

Other considerations	If the evidence allows, subgroups based on the severity of heart failure may be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. The availability and cost of biosimilar and generic products should be taken into account.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (2019) NICE technology appraisal 573 Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (2018) NICE technology appraisal 510 **Terminated appraisals:** Daratumumab with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (terminated appraisal) (2017) NICE technology appraisal 454 **Appraisals in development (including suspended appraisals):** Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable. NICE technology appraisal guidance ID1510. Publication date to be confirmed. Daratumumab in combination for untreated multiple myeloma when stem cell transplant is unsuitable. NICE technology appraisal guidance ID1492. Publication date to be confirmed. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma. NICE technology appraisal guidance ID2709. Expected publication date: 19 October 2022. Daratumumab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. NICE technology appraisal guidance ID3775. Suspended. Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma. NICE technology appraisal guidance ID1352. Suspended.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 46. Diagnostic service for amyloidosis (adults and children) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 2.

	https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

1. Amyloidosis Patient Information Site. Understanding AL Amyloidosis. [online, accessed March 2020]

2. Myeloma UK. AL amyloidosis. Available from: https://www.myeloma.org.uk/understanding-myeloma/related-conditions/al-amyloidosis/. [accessed January 2020]

3. Bayliss M, McCausland KL, Guthrie SD et al (2017) The burden of amyloid light chain amyloidosis on health-related quality of life. Orphanet Journal of Rare Diseases 12: 15.

4. Gertz MA. (2018) Immunoglobulin light chain amyloidosis: 2018 update on diagnosis, prognosis, and treatment. American Journal of Hematology 93(9): 1169-1180

5. Wechalekar AD, Gillmore JD, Bird J et al. on behalf of the BCSH Committee (2014) Guidelines on the management of AL amyloidosis. British Journal of Haematology 168: 186-206