Off-label drug use and safety of intravitreal anti-VEGF: data from Registries and Pharmacovigilance Network

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Background

According to EMA, off-label use "relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information." Off-label prescribing is not currently regulated at EU level but some countries adopted specific laws. In Italy, a comprehensive body of off-label legislation has been produced. L. 94/1998 allows the physician to use an off-label drug based on new efficacy data, but drug cost is not cover by NHS. L. 648/1996 establishes the reimbursement of a drug (1) approved in other countries, or (2) currently used in clinical trials or (3) used for not approved indications. All these drugs must be included in a list based on new scientific evidences resulting from at least phase II clinical trials.

Appropriateness in off-label drug prescriptions must be carefully assessed in order to ensure this use occurs only if data support a favorable risk/benefit profile.

Off-label use through intra-vitreal (ITV) injection of anti-vascular endothelial growth factor (anti-VEGF) drugs became an emblematic case of appropriateness. The Italian Medicines Agency (AIFA) initially added bevacizumab to the 648 list for various ITV indications but the use in age-related macular degeneration (AMD) was forbidden when ranibizumab came to reimbursement. Bevacizumab was then excluded from the list for all other off-label uses in 2012, following the introduction of safety warning in its summary of product characteristics (SPC), despite the same information were included in the SPC of ranibizumab as 'product-class-related adverse reactions'.

However, in 2013, the World Health Organization (WHO) included the off-label use of bevacizumab in AMD in its Essential Medicines List, and some studies excluded a difference in terms of risk/benefit profile compared to the approved drugs.

In 2014, bevacizumab was therefore re-introduced in Italy as a therapeutic option for AMD, following a decree which permits off-label use according to L. 648/1996 of less costly safe and effective drugs even in presence of authorized alternatives with higher cost.

Material and methods

We analyzed data from Registries and Pharmacovigilance Network between 2014 and 2016, in order to evaluate use of ITV anti-VEGF bevacizumab, ranibizumab and aflibercept and suspected adverse drug reactions (ADRs). We had access only to Sicilian databases.

Results

We found 25,188 prescriptions of anti-VEGF in Sicily, from 2014 to 2016 (Tab. 1), including 354 prescriptions of bevacizumab, 15,662 of ranibizumab and 9,172 of aflibercept.

A total of 64 ADRs (0.3% over anti-VEGF prescriptions) were reported in Sicily in the reference period (Tab. 2).

Out of the 59 ADRs reported with use of ranibizumab (0.4% over drug prescriptions), 40 were non-serious, 6 serious, 13 undefined (Fig. 1, Tab. 3). It is noteworthy that 85% of ADRs were treatment failures (Tab. 4).

Out of the 5 ADRs reported with aflibercept (0.05% over prescriptions) 3 were non-serious (treatment failures) and 2 serious (Fig. 2, Tab. 3 and 4). Tab. 5 shows ADRs per outcome.

No ADRs were reported with ITV use of bevacizumab.

Conclusions

Our data shows a limited ITV use of bevacizumab in Sicily (1.4% of anti-VEGF prescriptions), despite the re-admission in 648 list and despite the failure to show a lower risk/benefit profile compared to the available therapeutic options. Moreover, this is in contrast with data about off-label use before the removal of bevacizumab from 648 list in 2012. A low rate of ADRs has been found on Pharmacovigilance Network but it should be taken into account the phenomenon of under-reporting. These results should be compared with national data. The high percentage of treatment failures reported has to be further investigated.