Evidence based medicine in relation to different management modalities of age related macular degeneration

Essay

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ABSTRACT

The disease including; dietary vitamins & antioxidants, laser photocoagulation, radiotherapy, photodynamic therapy (PDT), intravitreal injection of triamcinolone acetonide, intravitreal injection of anti-VEGFs and surgical removal of the CNV. The effort in this work was aimed at collecting most of the clinical trials and studies done for management of AMD and at correlating them with evidence based medicine (EBM).Most of the studies is this essay are considered either level 1a or 2a regarding EBM.

KEY WORDS

Medicine
Modalities
Degeneration

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Table of Contents

List of Abbreviations

ARMD	Age Related Macular Degeneration
AMD	Age related Macular Degeneration
AREDS	Age Related Eye Disease Study
ANCHOR	Anti-VEGF Antibody for the Treatement of Predominantly Classic Choriodal Neovascularization in Age related macular degeneration
AE	Adverse Effects
ATE	Arterial Thromboembolic Effects
APTC	Antiplatele Trialists Collaboration
BCVA	Best Corrected Visual Acuity
CNV	Choroidal Neovascularisation
CFH	Complement Factor H
CFT	Central Foveal Thickness
CRT	Central Retinal Thickness
EBM	Evidence Based Medicine
FA	Flourescien Angiography
FAZ	Foveal Avascular Zone
GA	Geographic Atrophy
IVTA	Intravitreal Triamcinolone
ILM	Internal Limiting Membrane
LDL	Low Density Lipoprotein
MPS	Macular Photocoagulation Study
MIRA	Multicenter Investigation of Rheophoresis for AMD
MARINA	Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration
MI	Myocardial Infarction
NICE	National Institute of health & Clinical Excellence
OCT	Optical Coherence Tomography
PAS	Periodic Acid Schiff
PED	Pigment Epithelium Detachement
PDT	Photodynamic Therapy
PIER	Phase IIIB, multicenter, randomized,double-masked, sham injection– controlled study of the efficacy and safety of ranibizumab in patients with AMD-related subfoveal CNV.
PrONTO	Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab
RPE	Retinal Pigment Epithelium
RCA	Retinal to Choroidal Anastomosis
RD	Retinal Detachement
RCT	Randomized Controlled Trials
SRF	Subretinal fluid
SAE	Serious adverse effects
SR	Systematic Review
TAP	Treatment of AMD with Photodynamic therapy
VEGF	Vascular Endothelial Growth Factor
VISION	VEGF Inhibition Study In Ocular Neovascularisation
VA	Visual Acuity
VIP	Verteporfin In Photodynamic Therapy

List of figures

List of Tables

Introduction

Age-related macular degeneration is a leading cause of severe, irreversible vision impairment in developed[1, 2] as well as developing Countries.[3, 4] Although an estimated 80% of AMD patients have the non-neovascular form [2], the neovascular form is responsible for almost 80% to 90% of the severe visual loss (visual acuity 20/200 or worse) due to AMD.[5] The prevalence, incidence, and progression of AMD and most associated features (e.g., large drusen) increase with age.

Age-related macular degeneration (AMD) is a disorder of the macula and is characterized by one or more of the following: drusen formation, retinal pigment epithelium (RPE) abnormalities such as hypopigmentation or hyperpigmentation , geographic atrophy of the RPE and choriocapillaris neovascular (exudative) maculopathy.[6] Vascular endothelial growth factor A (VEGF-A) has been implicated in the pathogenesis of several ocular diseases, including age-related macular degeneration (AMD) and diabetic retinopathy. In humans, VEGF-A expression is increased in retinal pigment epithelial cells during the early stages of AMD, suggesting that VEGF-A plays a role in the initiation of neovascularization rather than being secondary to it. In addition, high concentrations of VEGF-A have been observed in excised choroidal neovascular membranes from AMD patients as well as in the vitreous humour of patients with subretinal choroidal neovascularization.[7] Further validation of VEGF-A as a target for therapeutic intervention in neovascular AMD has come from several well-controlled randomized clinical trials involving 2 different antiangiogenic drugs: Pegaptanib sodium injection (Macugen, OSI-Eyetech Pharmaceuticals, New York, NY)[8] and ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA).[9]

Management options for AMD include observation, antioxidants vitamin and mineral supplements, cessation of smoking, intravitreal injection of anti-VEGF agents, photodynamic therapy (PDT) , and laser photocoagulation surgery.[10] Many studies have investigated the different lines of management of AMD; several of these were multi-centred controlled trials, which provided evidence on the different modes of management.

Evidence-based medicine has been defined as "the process of systematically finding, appraising and using contemporaneous research findings as the basis for clinical decisions."[11] Evidence based medicine, remains a hot topic for clinicians, public health practitioners, purchasers, planners and the public. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. Without clinical expertise, practice risks becoming tyrannized by evidence, for even excellent external evidence may be inapplicable or inappropriate for an individual patient. Thus, evidence based medicine, being not restricted to randomized trials and meta-analyses, involves tracking down the best external evidence with which to answer our clinical questions. It proves to be the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.[12]

Aim of work

The aim of this work is to review the clinical studies and reports and identify the currently available evidence relating to different management modalities of age related macular degeneration.

Evidence Based Medicine

- **Levels of EBM.**

- **Research methods recognized in EBM.**

Evidence Based Medicine

Evidence Based Medicine (EBM) is defined as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.[12] It is also defined as the process of systematically finding, appraising and using contemporary research findings as the basis for clinical decisions.[13]

Evidence based medicine is based on five linked principles: ***firstly***, clinical decisions should be based on the best available scientific evidence; ***secondly***, the clinical problem should determine the type of evidence to be sought; ***thirdly***, identifying the best evidence means using epidemiological and biostatistical ways of thinking; ***fourthly***, conclusions derived from identifying and critically appraising evidence are useful only if put into action in managing patients or making health care decisions; and, ***finally***, performance should be constantly evaluated.[14]

These principles can be translated into steps as follows:

1. Convert the need for information into clinically relevant, answerable questions
2. Find, in the most efficient way, the best evidence with which to answer these questions (whether this evidence comes from clinical examination, laboratory tests, published research, or other sources)
3. Critically appraise the evidence for its validity (closeness to the truth) and usefulness (clinical applicability)
4. Integrate the appraisal with clinical expertise and apply the results to clinical practice
5. Evaluate your performance.[15]

A disadvantage of evidence based medicine is that it takes time to find the evidence and use it.[13] As a result; clinical guidelines are increasingly being published by bodies like the Royal College of Ophthalmologists and the American Academy of Ophthalmology.[16,17] An expert committee does the work of shifting through the scientific literature for clinicians and offers coherently sequenced recommendations based on the best available evidence aimed at everyday decision-making situations. Guidelines can be applied to any aspect of clinical care: how and when to order diagnostic or screening tests, when to provide certain medical services, how these should be performed, and how long patients should remain hospitalized following a procedure.[18] Guidelines must be continually updated to take account of changes in medical knowledge and practice and particularly the results of randomised trials and meta-analysis. By indicating areas in which evidence is incomplete or inadequate, they can help to identify priorities for research and by pointing out where evidence is strong, they can improve care for patients.[19]

Levels of Evidence:

Not all evidence is of the same strength and therefore there are different levels of evidence. The strength of evidence depends on the research methods and the number of the studies that have provided the evidence. A variety of grading systems for evidence are currently in use. The system used is usually defined at the beginning of any guidelines publication. An example of a grading system for evidence is that recommended by the Centre of Evidence Based System in the University of Oxford.

A summary of its levels of evidence for therapy and prevention is as follows:

Level 1a is when the evidence is based on a systematic review (SR) of randomised controlled studies (RCTs)

Level 1b is when the evidence is based on an individual RCT

Level 2a is when the evidence is based on an SR of cohort studies

Level 2b is when the evidence is based on an individual cohort study

Level 3a is when the evidence is based on an SR of case-control studies

Level 3b is when the evidence is based on an individual case-control study

Level 4 is when the evidence is based on case-series

Level 5 is when the evidence is based on expert opinion.[20]

Research Methods Recognized in EBM:

- Systematic Review:

A systematic review is a formalised and strict process of combining the information from all relevant studies (both published and unpublished) of the same health condition; these studies are usually clinical trials of the same or similar treatments but may be observational studies. So important is its role in EBM that it has become the focus of an international network of clinicians, methodologists and consumers who have formed the Cochrane Collaboration. They have created the Controlled Cochrane Trials Register and publish continually updated systematic reviews.[21]

- Meta-analysis:

A meta-analysis is a particular type of systematic review that focuses on the numerical results whose main aim is to combine the results from individual studies to produce an overall or average result.[21]

- Randomized Controlled Trial:

RCT is an experiment performed on human subjects to assess the efficacy of a new treatment. The new treatment is given to a group of patients (called the treated group) and another treatment, usually the most widely used, is given to another group of

patients at the same time (the control group).RCTs are either open label, blind or double blind. Patients are allocated to one group or another by randomisation.[22]

- Cohort Study:

Cohort Studies involve following groups of subjects over time. Their purpose is to describe the occurrence of certain outcomes over time and to analyse associations between predictors and those outcomes. They can be prospective or retrospective.[23]

- Case-Control Study:

In a case-control study, individuals with a particular condition or disease (the cases) are selected for comparison with a series of individuals in which the condition or disease is absent (the controls). Cases and controls are compared with respect to existing or past attributes or exposures thought to be relevant to the development of the condition or disease under study.[24]

- Case Series:

A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. A case series can be retrospective or prospective and usually involves a smaller number of patients than the more powerful case-control studies or randomized controlled trials.[25]

Pathology & Clinical picture of AMD

- **Pathology of AMD.**
- **Classification of AMD.**
- **Natural history of AMD.**
- **Clinical picture of AMD.**