The Top 100 Most-Cited Papers on Intravitreal Injections: A Bibliographic Perspective

Purpose: To analyze the top 100 most-cited papers on pars intravitreal injections.

Methods: Literature search using the bibliographic databases of the ISI Web of Knowledge for all types of publications on intravitreal injections published between 1965 and 2019 in peer-reviewed journals.

Results: Eighty-three of the top 100 papers on intravitreal injections were published in ophthalmology journals, their majority in the top five Q1 leading journals in the field. They originated from 16 different countries, predominantly from the USA (n=52), and were all published in English. These manuscripts cover a wide spectrum of topics but were mostly focused on retinal diseases (n=60) and the use of anti-VEGF or steroid agents (n=75).

Discussion: This bibliographic study provides a unique perspective on the evolution and assimilation of intravitreal injections, from their introduction, through their present role as the most common therapeutic procedure in ophthalmology, to future developments.

Keywords: bibliography, citation, historical, intravitreal injection

Introduction

Intravitreal injections are currently an integral part of the practice of ophthalmology, and are a widely accepted method for intraocular drug delivery. Until only 15 years ago, this procedure was performed much less frequently, and was reserved for delivering antibiotics in cases of endophthalmitis or steroids in patients with macular edema. Following the introduction of anti-Vascular Endothelial Growth Factor (VEGF) agents, the use of intravitreal injections increased exponentially, and they quickly became the most commonly performed procedure in ophthalmology.

The first anti-VEGF agent to be approved by the FDA was pegaptanib sodium (Macugen, Pfizer), which was effective in improving visual acuity in patients with neovascular age-related macular degeneration (AMD), but as it only inhibited one isoform of VEGF-A it is no longer used. Soon after ranibizumab (Lucentis, Genentech) was developed, and demonstrated excellent results in treating neovascular AMD in the seminal MARINA and ANCHOR studies. Other anti-VEGF agents in common use are bevacizumab (Avastin, Genentech), which is extensively used off-label for economic reasons, and aflibercept (Eylea, Regeneron). The efficacy and excellent safety profile of anti-VEGF agents administered by intravitreal injections has been demonstrated in numerous large-scale randomized controlled trials, for a wide variety of retinal diseases, including neovascular AMD, diabetic macular edema (DME), and retinal vein occlusions (RVOs).
The introduction of anti-VEGF agents has led to no less than a revolution in the practice of ophthalmology. Not only has the procedure changed from a rarely performed technique to the standard of care in numerous retinal diseases, it also achieved much greater success in visual improvement and maintenance than previously available treatment modalities, such as macular laser and photodynamic therapy (PDT), which became almost obsolete. The purpose of this study was to review the literature on intravitreal injections, identify the 100 most-cited papers on this topic, and provide a bibliographic-historic perspective on this important technique which has had an enormous effect on the practice of ophthalmology.

Methods
A comprehensive search of the bibliographic databases of the ISI Web of Knowledge databases (Web of Science core collection and Medline) was performed for the purpose of this study, by an expert medical librarian. The search was performed using the combination of “intravitreal injection” as the keywords. The search included all peer-reviewed journals, and was not limited to the field of ophthalmology. The search included all publications from 1965 (the earliest year available in the databases) to the present (it was conducted on June 1st 2019). All types of publications were included.

The gross results of the search were then analyzed for their type, journal and year of publication, country of origin and language. The results were listed according to the number of total citations, and were then reviewed individually by the authors. The authors read the abstracts and if additional information was required then the manuscripts were reviewed in full. Manuscripts were excluded if they were found not to focus on intravitreal injections or have any relevance to ophthalmology. For example, a paper in which intravitreal injections of a labeling agent was used as a technique for a neuroscience experiment was not included.10 Included manuscripts had to focus on intravitreal injection as a therapeutic technique, therefore studies in which intravitreal injection was only used as a technique to create a model were also excluded. For example, a study in which intravitreal injections of ouabain were used to induce retinal damage in zebrafish that were later followed for spontaneous regeneration was excluded.11 Using these criteria, a list of the 100 most-cited manuscripts on intravitreal injections was achieved. For each of the manuscripts on the list, the following details were recorded: overall number of citations, mean citations per year since publication, journal name, year of publication, names of first and last authors, number of authors, country of origin, type of manuscript, number of patients/eyes included, the main topic, and the agents used in the intravitreal injection. Manuscript types were categorized into clinical studies, animal studies, laboratory experiments, reviews, meta-analyses, and case reports.

Correlations between continuous variables were analyzed using Pearson’s correlation coefficient, and T-tests and Analysis of Variance (ANOVA) were used to analyze associations between categorical parameters. A P-value of 0.05 was used to determine statistical significance. Data was analyzed using SPSS for Windows version 20.

Results
The overall search results yielded 5486 published manuscripts. Of these, the top 100 manuscripts on intravitreal injections were identified following the analysis and inclusion criteria detailed above.

Overall Literature on Intravitreal Injections
Between January 1, 1965 and June 1, 2019, a total of 5486 manuscripts were published on the topic of intravitreal injections. These papers had a total of 113,588 citations, with a mean of 20.69 citations per paper. The number of publications was very low until 2004, and since that year the number of publications on intravitreal injections and their citations have increased significantly and continuously (Figure 1).

Almost two-thirds (63.7%) of the manuscripts were published in Ophthalmology journals, with 82.9% of them being original articles and 7.5% reviews. 95.5% of the manuscripts were published in English, 2.5% in German, and 1.3% in French. About a third (32.1%) of the manuscripts originated from the USA, followed by China, Japan, and Germany. Details of this gross distribution are presented in Figure 2.

The Top 100 Manuscripts on Intravitreal Injections
The top 100 papers on intravitreal injections are listed in order of descending number of citations in Table 1. The mean number of citations was 235±136, with a median of 173 citations and a range of 128 to 960 citations.

Of the top 100 papers on intravitreal injections, 83 were published in ophthalmology journals. These journals
include *Ophthalmology* (n=17), *Retina* (n=17), *American Journal of Ophthalmology* (n=12), *Investigative Ophthalmology and Visual Science* (n=12), *Archives of Ophthalmology* (n=9), *British Journal of Ophthalmology* (n=5), *Ophthalmic Surgery and Lasers* (n=2), *Survey of Ophthalmology* (n=2), *Australian and New Zealand Journal of Ophthalmology* (n=2), *Graefes Archive for Clinical and Experimental Ophthalmology* (n=1), *Eye* (n=1), *Experimental Eye Research* (n=1), *Clinical and Experimental Ophthalmology* (n=1), and *Current Opinion in Ophthalmology* (n=1). Two-thirds (67) of the papers were published in five of the leading Q1 (at the time of publication) journals in Ophthalmology – *Ophthalmology, Retina, American Journal of Ophthalmology, Investigative Ophthalmology and Visual Science,* and *Archives of Ophthalmology*. All papers were written in English. Additionally, 15 of the papers were also presented at international meetings registered at the ISI Web of Knowledge databases, most often at the AAO or ARVO annual conferences.

Figure 1 The number of publications on intravitreal injections per year between 1995–2019. Note the significant increase starting in 2004.

Figure 2 Distribution of the top 100 publications on intravitreal injections, by country of origin (A), language (B), journal field (C), and publication type (D).
| Source Title | Authors | Total Citations | Average per Year | Year |
|--------------|---------|-----------------|------------------|------|
| Intraocular lens in-vivo by inhibition of VEGF receptor-chimeric proteins | Martinell, A. Dolcini, JS; Greenberg, PB; Rogers, AH; Puliafito, CA; Reichel, E; Bualini, C | 661 | 1992 | Ophthalmology |
| Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) (R) for neovascular age-related macular degeneration | Livadi, MM; Uozumi, K; Yasumura, D; Matthes, MT; Yancopoulos, GD; Sornberg, RH | 575 | 2006 | Retina – The Journal of Retinal and Vitreous Disease |
| Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration | Ferrari, N; Damico, L; Shams, N; Lowman, H; Kan, R | 497 | 2006 | Retina – The Journal of Retinal and Vitreous Disease |
| Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration | Ferrari, L; Bursell, SE; Clermont, A; Duh, E; Ishi, H; Takagi, C; Mori, F; Cialla, TA; Ways, K; Jroussak, M; Smith, LEH; King, GL | 483 | 1997 | Diabetes |
| Pharmacokinetics of intravitreal bevacizumab (Avastin) in the treatment of specific ocular pathologies | Adams, AP; Shima, DT; Tolentino, MJ; Gragoudas, ES; Ferrara, N; Folkman, J; Damico, PA; Miller, JW | 460 | 1996 | Archives of Ophthalmology |
| Intravitreal bevacizumab (Avastin) in the treatment of neovascular disease | Avary, RL; Pearse, P; Parameswaran, DJ; Rabena, MD; Castellani, AA; Nair, MA; Guat, MJ; Wender, R; Patel, A | 455 | 2006 | Ophthalmology |
| Pharmacokinetics of intravitreal bevacizumab (Avastin) | Bakkal, SS; Snyder, MR; Reid, PM; Pulito, JS; Singh, RJ | 428 | 2007 | Ophthalmology |
| Title                                                                 | Authors                                                                 | Journal                                      | Year | Volume | Page | Impact Factor |
|----------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------|------|--------|------|---------------|
| Intravitreal injection of triamcinolone for diffuse diabetic macular edema | Jonas, JB; Kreissig, I; Sofker, A; Degenring, RF                         | Archives of Ophthalmology                   | 2003 | 396    | 23.29|               |
| Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection | Beer, PM; Bakri, SJ; Singh, RJ; Liu, WG; Peters, GB; Miller, M           | Ophthalmology                               | 2003 | 355    | 20.88|               |
| Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin (R)) for macular edema from central retinal vein occlusion | Rosenfeld, PJ; Fung, AE; Puliafito, CA                                  | Ophthalmic Surgery Lasers & Imaging         | 2005 | 354    | 23.6 |               |
| Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion – A short-term study | Iturralde, D; Spaide, RF; Meyerle, CB; Klancnik, JM; Yannuzzi, LA; Fisher, YL; Sorenson, J; Slakter, JS; Freund, KB; Cooney, M; Fine, HF | Retina – The Journal of Retinal and Vitreous Diseases | 2006 | 343    | 24.5 |               |
| Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage | Spaide, RF; Fisher, YL                                                  | Retina – The Journal of Retinal and Vitreous Diseases | 2006 | 342    | 24.43|               |
| Intravitreal triamcinolone acetonide in exudative age-related macular degeneration | Danis, RP; Ciulla, TA; Pratt, LM; Aniker, W                             | Retina – The Journal of Retinal and Vitreous Diseases | 2000 | 339    | 16.95|               |
| Intravitreal triamcinolone for uveitic cystoid macular edema: An optical coherence tomography study | Antcliff, RJ; Spalton, DJ; Stanford, MR; Graham, EM; Fytyche, TJ; Marshall, J | Ophthalmology                               | 2001 | 313    | 16.47|               |
| Basic fibroblast growth-factor and local injury protect photoreceptors from light damage in the rat | Faktorovitch, EG; Steinberg, RH; Yasumura, D; Matthes, MT; Lavaul, MM    | Journal of Neuroscience                       | 1992 | 312    | 11.14|               |
| Intravitreal injection of crystalline cortisone as adjunctive treatment of diabetic macular edema | Jonas, JB; Sofker, A                                                    | American Journal of Ophthalmology          | 2001 | 307    | 16.16|               |
| Intravitreal triamcinolone acetonide for diabetic diffuse macular edema - Preliminary results of a prospective controlled trial | Massin, P; Audren, F; Hauchine, B; Erginay, A; Bergmann, JF; Benosman, R; Caulin, C; Gaudric, A | Ophthalmology                               | 2004 | 304    | 19   |               |
| Enzymatic vitreolysis with ocirplasmin for vitreomacular traction and macular holes | Stalmans, P; Benz, MS.; Gandorfer, A; Kampik, A; Girach, A; Pakola, S; Haller, JA | New England Journal of Medicine             | 2012 | 301    | 37.63|               |
| Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema | Haritoglou, C; Kook, D; Neubauer, A; Wolf, A; Priglinger, S; Strauss, R; Gandorfer, A; Ulbig, M; Kampik, A | Retina – The Journal of Retinal and Vitreous Diseases | 2006 | 293    | 20.93|               |
| Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide | Tana, Y; Chandler, D; Machemer, R                                       | American Journal of Ophthalmology          | 1980 | 283    | 7.08 |               |

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Table I (Continued).

| Title                                                                                     | Authors                                           | Source Title             | Publication Year | Total Citations | Average per Year |
|-------------------------------------------------------------------------------------------|---------------------------------------------------|--------------------------|------------------|------------------|------------------|
| A Phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema | Scott, IU; Edwards, AR; Beck, RW; Bressler, NM; Chan, CK; Elman, MJ; Friedman, SM; Greven, CM; Maturi, RK; Pieramici, DJ; Shami, M; Singerman, L; Stockdale, CR | Ophthalmology           | 2007             | 280              | 21.54            |
| Intraocular pressure after intravitreal injection of triamcinolone acetonide             | Jonas, JB; Kreissig, I; Degenring, R               | British Journal of Ophthalmology | 2003             | 279              | 16.41            |
| Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin) | Shahar, J; Avery, RL; Heilweil, G Barak, A; Zemel, E; Lewis, GP; Johnson, PT; Fisher, SK; Perlman, I; Loewenstein, A | Retina – Retinal and Vitreous Diseases | 2006             | 279              | 19.93            |
| Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis  | Young, S; Larkin, G; Branley, M; Lightman, S      | Clinical and Experimental Ophthalmology | 2001             | 268              | 14.11            |
| Acute endophthalmitis following intravitreal triamcinolone acetonide injection           | Moshfeghi, DM; Kaiser, PK; Scott, IU; Sears, JE; Benz, M; Sinesterra, JP; Kaiser, RS; Bakri, S; Maturi, RK; Belmont, J; Beer, PM; Murray, TG; Quiroz-Mercado, H; Mieler, WF | American Journal of Ophthalmology | 2003             | 267              | 15.71            |
| Treatment of the adult retina with microglia-suppressing factors retards axotomy-induced neuronal degradation and enhances axonal regeneration in vivo and in vitro | Thanos, S; Mey, J; Wäld, M                         | Journal of Neuroscience   | 1993             | 261              | 9.67             |
| A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration - One year results | Gillies, MC; Simpson, JM; Luo, W; Penfold, P; Hunyor, ABL; Chua, W; Mitchell, P; Bilson, F | Archives of Ophthalmology | 2003             | 245              | 14.41            |
| Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of I-125-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration | Mordenti, J; Cuthbertson, RA; Ferrara, N; Thomsen, K; Berleau, L; Licko, V; Allen, PC; Valverde, CR; Meng, YG; Fei, DTW; Fourre, KM; Ryan, AM | Toxicologic Pathology     | 1999             | 243              | 11.57            |
| Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration | Bashshur, ZF; Bazarbachi, A; Schakal, A; Haddad, ZA; El Habib, CP; Noureddin, BM | American Journal of Ophthalmology | 2006             | 240              | 17.14            |
| Intraocular pressure elevation after intravitreal triamcinolone acetonide injection       | Jonas, JB; Degenring, RF; Kreissig, I; Akkoyun, I; Kamppeter, BA | Ophthalmology            | 2005             | 238              | 15.87            |
| Title                                                                 | Authors                                                                 | Journal                                                                 | Year | Volume | Impact Factor |
|----------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------|---------|---------------|
| Gene therapy with brain-derived neurotrophic factor as a protection: Retinal ganglion cells in a rat glaucoma model | Martin, KRG; Quigley, HA; Zack, DJ; Levkovitch-Verbin, H; Kielczewski, J; Valenta, D; Baumrind, L; Pease, ME; Klein, RL; Hauswirth, WW | Investigative Ophthalmology & Visual Science                           | 2003 | 231     | 13.59         |
| Exudative macular degeneration and intravitreal triamcinolone: 18 month follow up | Challa, JK; Gillies, MC; Penfold, PL; Gyory, JF; Hunyor, ABL; Billson, FA | Australian and New Zealand Journal of Ophthalmology                   | 1998 | 227     | 10.32         |
| Testing intravitreal toxicity of bevacizumab (Avastin)               | Manzano, RPA; Peyman, GA; Khan, P; Kivlicim, M                           | Retina – The Journal of Retinal and Vitreous Diseases                   | 2006 | 227     | 16.21         |
| Primary intravitreal bevacizumab (Avastin) for diabetic macular edema – Results from the Pan-American Collaborative Retina Study Group at 6-month follow-up | Arevalo, JF; Fromow-Guerra, J; Quiroz-Mercado, H; Sanchez, JG; Wu, L; Maia, M; Berrocal, MH; Solis-Vivancol, A; Farah, ME | Ophthalmology                                                           | 2007 | 224     | 17.23         |
| Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy | Arevalo, JF; Maia, M; Flynn, HW, Jr; Saravia, M; Avery, RL; Wu, L; Farah, M; Eid; Pieramici, DJ; Berrocal, MH; Sanchez, JG | British Journal of Ophthalmology                                      | 2008 | 222     | 18.5          |
| Combined photodynamic therapy with verteporfin and intravitreal triamcinolone acetonide for choroidal neovascularization | Spaid, RF; Sorenson, J; Maranan, L                                       | Ophthalmology                                                           | 2003 | 220     | 12.94         |
| Neurotrophic factors cause activation of intracellular signaling pathways in Muller cells and other cells of the inner retina, but not photoreceptors | Wahlin, KJ; Campochiaro, PA; Zack, DJ; Adler, R                          | Investigative Ophthalmology & Visual Science                           | 2000 | 213     | 10.65         |
| Safety of an intravitreal injection of triamcinolone – Results from a randomized clinical trial | Gillies, MC; Simpson, JM; Billson, FA; Luo, W; Penfold, P; Chua, W; Mitchell, P; Zhu, MD; Hunyor, ABL | Archives of Ophthalmology                                             | 2004 | 213     | 13.31         |
| Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans | Krophne, TU; Eter, N; Holz, FG; Meyer, CH                                | American Journal of Ophthalmology                                     | 2008 | 208     | 17.33         |
| N-methyl-D-aspartate (NMDA)-induced apoptosis in rat retina          | Lam, TT; Abler, AS; Kwong, JMK; Tso, MOM                                 | Investigative Ophthalmology & Visual Science                           | 1999 | 205     | 9.76          |
| Ciliary neurotrophic factor and stress stimuli activate the Jak-STAT pathway in retinal neurons and glia | Peterson, WM; Wang, Q; Tzekova, R; Wieand, SJ                            | Journal of Neuroscience                                               | 2000 | 197     | 9.85          |

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| Title                                                                 | Authors                                                                 | Source Title                                                                 | Publication Year | Total Citations | Average per Year |
|----------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------|-----------------|------------------|
| Penetration of bevacizumab through the retina after intravitreal     | Heiduschka, P; Fietz, H; Hofmeister, S; Schultheiss, S; Mack, AF; Peters, S; Ziemssen, F; Niggemann, B; Julien, S; Bartz-Schmidt, KU; Schraermeyer, U | Investigative Ophthalmology & Visual Science                                | 2007             | 192             | 14.77            |
| injection in the monkey                                              |                                                                        |                                                                             |                  |                 |                  |
| Photodynamic therapy with verteporfin combined with intravitreal     | Spaide, RF; Sorenson, J; Maranan, L                                      | Ophthalmology                                                               | 2005             | 190             | 12.67            |
| injection of triamcinolone acetonide for choroidal                   |                                                                        |                                                                             |                  |                 |                  |
| neovascularization                                                   |                                                                        |                                                                             |                  |                 |                  |
| Dexamethasone intravitreal implant for treatment of diabetic          | Boyer, DS; Faber, D; Gupta, S; Patel, SS; Tabandeh, H; Li, X-Y; Liu, CC; Lou, J; Whitcup, SM | Retina-the Journal of Retinal and Vitreous Diseases                          | 2011             | 186             | 20.67            |
| macular edema in vitrectomized patients                              |                                                                        |                                                                             |                  |                 |                  |
| Efficacy of intravitreal bevacizumab for polypoidal choroidal        | Gomi, F; Sawa, M; Sakaguchi, H; Tsujikawa, M; Oshima, Y; Kamei, M; Tano, Y | British Journal of Ophthalmology                                           | 2008             | 182             | 15.17            |
| vasculopathy                                                         |                                                                        |                                                                             |                  |                 |                  |
| Noninfectious endophthalmitis associated with intravitreal           | Roth, DB; Chieh, J; Spirm, MJ; Green, SN; Yarian, DL; Chaudhry, NA      | Archives of Ophthalmology                                                  | 2003             | 176             | 10.35            |
| triamcinolone injection                                              |                                                                        |                                                                             |                  |                 |                  |
| Maximum tolerated dose of a humanized anti-vascular                 | Rosenfeld, PJ; Schwartz, SD; Blumenkranz, MS; Miller, JW; Haller, JA; Reimann, JD; Greene, WL; Shams, N | Ophthalmology                                                           | 2005             | 173             | 11.53            |
| endothelial growth factor antibody fragment for treating             |                                                                        |                                                                             |                  |                 |                  |
| neovascular age-related macular degeneration                          |                                                                        |                                                                             |                  |                 |                  |
| Adverse events and complications associated with intravitreal        | Falavarjani, KG; Nguyen, QD                                              | Eye                                                                        | 2013             | 173             | 24.71            |
| injection of anti-VEGF agents: a review of literature               |                                                                        |                                                                             |                  |                 |                  |
| Adenovirus-mediated gene transfer of ciliary neurotrophic factor can | Cayouette, M; Gravel, C                                                  | Human Gene Therapy                                                        | 1997             | 172             | 7.48             |
| prevent photoreceptor degeneration in the retinal degeneration (rd) mouse |                                                                      |                                                                             |                  |                 |                  |
| Intravitreal triamcinolone acetonide for exudative age related       | Jonas, JB; Kreissig, I; Hugger, P; Sauder, G; Panda-Jonas, S; Degenring, R | British Journal of Ophthalmology                                           | 2003             | 172             | 10.12            |
| macular degeneration                                                 |                                                                        |                                                                             |                  |                 |                  |
| Meta-analysis of endophthalmitis after intravitreal injection of     | McCannel, CA                                                            | Retina – The Journal of Retinal and Vitreous Diseases                      | 2011             | 171             | 19               |
| anti-vascular endothelial growth factor agents causative             |                                                                        |                                                                             |                  |                 |                  |
| organisms and possible prevention strategies                          |                                                                        |                                                                             |                  |                 |                  |
| MicroRNA-200b regulates vascular endothelial growth factor-         | McArthur, K; Feng, B; Wu, Y; Chen, S; Chakrabarti, S                   | Diabetes                                                                   | 2011             | 171             | 19               |
| mediated Alterations in diabetic retinopathy                          |                                                                        |                                                                             |                  |                 |                  |
| Title                                                                 | Authors                                                                 | Journal                                      | Year | Volume | Pages | Impact Factor |
|----------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------|------|--------|--------|---------------|
| Association of endothelin-I with normal-tension glaucoma – clinical and fundamental-studies | Sugiyama, T; Moriya, S; Oku, H; Azuma, I                              | Survey of Ophthalmology                      | 1995 | 170    | 6.8    |               |
| Exudative macular degeneration and intravitreal triamcinolone – A pilot study | Penfold, PL; Gyory, JF; Hunyor, AB; Billson, FA                        | Australian and New Zealand Journal of Ophthalmology | 1995 | 170    | 6.8    |               |
| Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment – Three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial | Sutter, FKP; Simpson, JM; Gillies, MC                                 | Ophthalmology                               | 2004 | 170    | 10.63   |               |
| Long-term protection of retinal structure but not function using RAAV/CNTF in animal models of retinitis pigmentosa | Liang, FQ; Aleman, TS; Dejneka, NS; Dudus, L; Fisher, KJ; Maguire, AM; Jacobson, SG; Bennett, J | Molecular Therapy                            | 2001 | 168    | 8.84   |               |
| Intravitreal triamcinolone acetonide in eyes with cystoid macular edema associated with central retinal vein occlusion | Park, CH; Jaffe, GJ; Fekrat, S                                         | American Journal of Ophthalmology           | 2003 | 166    | 9.76   |               |
| Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration – Phase II study results | Fish, G; Haller, JA; Ho, AC; Klein, M; Loewenstein, J; Martin, D; Orth, D; Rosen, RB; Sanislo, S; Schwartz, SD; Singerman, LJ; Williams, G; Adams, AP; Blumenkranz, M; Goldberg, M; Gragoudas, ES; Miller, JW; Yannuzzi, L; Guyer, DR; O’Shaughnessy, D; Patel, S | Ophthalmology                               | 2003 | 165    | 9.71   |               |
| Intravitreal injection of dexamethasone – treatment of experimentally induced endophthalmitis | Graham, RO; Peyman, GA                                               | Archives of Ophthalmology                   | 1974 | 163    | 3.54   |               |
| Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative diabetic retinopathy | Jonas, JB; Hayler, JK; Soarker, A; Panda-Jonas, S                     | American Journal of Ophthalmology          | 2001 | 163    | 8.58   |               |
| Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown | Edelman, JL; Lutz, D; Castro, MR                                       | Experimental Eye Research                   | 2005 | 162    | 10.8   |               |
| Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab | Peters, S; Heiduschka, P; Julien, S; Ziemssen, F; Fietz, H; Bartz-Schmidt, KU; Schraermeyer, U | American Journal of Ophthalmology          | 2007 | 161    | 12.38  |               |
| Macular edema                                                                 | Tranos, PG; Wickremasinghe, SS; Stangos, NT; Topouzis, F; Tsinopoulos, L; Pavesio, CE | Survey of Ophthalmology                     | 2004 | 159    | 9.94   |               |
| AAV-mediated expression of CNTF promotes long-term survival and regeneration of adult rat retinal ganglion cells | Leaver, SG; Cui, Q; Plant, GW; Arulpragasam, A; Hisheh, S; Verhaegen, J; Harvey, AR | Gene Therapy                                | 2006 | 159    | 11.36  |               |

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Table 1 (Continued).

| Title                                                                 | Authors                                                                 | Source Title                                      | Publication Year | Total Citations | Average per Year |
|----------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------|------------------|------------------|------------------|
| Long-term benefit of sustained-delivery fluocinolone acetonide vitreous Inserts for diabetic macular edema | Campochiaro, PA; Brown, DM; Pearson, A; Ciulla, T; Boyer, D; Holz, FG; Tolentino, M; Gupta, A; Duarte, L; Madreperla, S; Gonder, J; Kapik, B; Billman, KN; Kane, FE | Ophthalmology                                      | 2011             | 158              | 17.56            |
| In vivo protection of photoreceptors from light damage by pigment epithelium-derived factor | Cao, W; Tombran-Tink, J; Elias, R; Sezate, S; Mrazek, D; McGinnis, JF | Investigative Ophthalmology & Visual Science      | 2001             | 154              | 8.11             |
| Potential role of microglia in retinal blood vessel formation        | Checchin, D; Sennlaub, F; Leevasseur, E; Leduc, M; Chemtob, S           | Investigative Ophthalmology & Visual Science      | 2006             | 154              | 11               |
| Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE Study) | Jorge, R; Costa, RA; Comt, DC; Cintra, LP; Scott, IJ | Retina – The Journal of Retinal and Vitreous Diseases | 2006             | 153              | 10.93            |
| Intravitreal triamcinolone acetonide as treatment of macular edema in central retinal vein occlusion | Jonas, JB; Kreissig, I; Degenring, RF | Graefes Archive for Clinical and Experimental Ophthalmology | 2002             | 152              | 8.44             |
| Pharmacokinetics of bevacizumab after topical, subconjunctival, and intravitreal administration in rabbits | Nomoto, H; Shiraga, F; Kuno, N; Kimura, E; Fujii, S; Shinomiya, K; Nugent, AK; Hirooka, K; Baba, T | Investigative Ophthalmology & Visual Science | 2009             | 152              | 13.82            |
| Serum concentrations of bevacizumab (Avastin) and vascular endothelial Growth factor in infants with retinopathy of prematurity | Sato, T; Wada, K; Arahori, H; Kuno, N; Imoto, K; Iwahashi-Shima, C; Kusaka, S | American Journal of Ophthalmology                | 2012             | 152              | 19               |
| Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II | Mintz-Hittner, HA; Kuffel, RR | Retina – The Journal of Retinal and Vitreous Diseases | 2008             | 151              | 12.58            |
| Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab | Bakall, B; Folk, JC; Boldt, HC; Sohn, EH; Stone, EM; Russell, SR; Mahajan, VB | American Journal of Ophthalmology                | 2013             | 149              | 21.29            |
| Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative vitreoretinopathy | Jonas, JB; Hayler, JK; Panda-Jonas, S | British Journal of Ophthalmology                 | 2000             | 148              | 7.4              |
| Study Title                                                                 | Authors                                                                 | Journal/Source                                      | Year | Vol | Impact Factor |
|----------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------|------|-----|---------------|
| Encapsulation of dexamethasone into biodegradable polymeric nanoparticles  | Gomez-Graete, C; Tsapis, N; Besnard, M; Bochot, A; Fattal, E           | International Journal of Pharmaceutics               | 2007 | 146 | 11.23         |
| Intravitreal triamcinolone acetonide inhibits choroidal neovascularization in a laser-treated rat model | Ciulla, TA; Criswell, MH; Danis, RP; Hill, TE                           | Archives of Ophthalmology                           | 2001 | 144 | 7.58          |
| Neuroprotective effect of (-)delta-9-tetrahydrocannabinol and cannabidiol in N-methyl-D-aspartate-induced retinal neurotoxicity – Involvement of peroxynitrite | El-Remessy, AB; Khalil, IE; Matragoon, S; Abou-Mohamed, G; Tsai, NJ; Roon, P; Caldwell, RB; Caldwell, RW; Green, K; Liou, GI | American Journal of Pathology                       | 2003 | 143 | 8.41          |
| Intravitreal triamcinolone for the treatment of macular edema associated with central retinal vein occlusion | Ip, MS; Gottlieb, ML; Kahana, A; Scott, IU; Altaweel, MM; Blodi, BA; Gangnon, RE; Poliafito, CA | Archives of Ophthalmology                           | 2004 | 143 | 8.94          |
| Anti-vascular endothelial growth factor for neovascular age-related macular degeneration | Solomon, SD; Lindsley, pistina; Vedula, SS; Krzyzolik, MG; Hawkins, BS | Cochrane Database of Systematic Reviews              | 2014 | 142 | 23.67         |
| Endotoxin-induced uveitis in the rat – the significance of intraocular interleukin-6 | Hoekzema, R; Verhagen, C; Vanharen, M; Kijlstra, A                      | Investigative Ophthalmology & Visual Science        | 1992 | 141 | 5.04          |
| Peroxisome proliferator-activated receptor-gamma ligands inhibit choroidal neovascularization | Murata, T; H, SK; Hangai, M; Ishibashi, T; Xi, XP; Kim, S; Hsueh, WA; Ryan, SJ; Law, RE; Hinton, DR | Investigative Ophthalmology & Visual Science        | 2000 | 141 | 7.05          |
| Intravitreal injection of erythropoietin protects both retinal vascular and neuronal cells in early diabetes | Zhang, J; Wu, Y; Jin, Y; Ji, F; Sindair, SH; Luo, Y; Xu, G; Lu, Lu; Dai, W; Yanoff, M; Li, W; Xu, GT | Investigative Ophthalmology & Visual Science        | 2008 | 141 | 11.75         |
| Evaluation of the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection | Kwak, HW; Damico, DJ                                                   | Archives of Ophthalmology                           | 1992 | 140 | 5             |
| Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement | Smith, JR; Rosenbaum, JT; Wilson, DJ; Doolittle, ND; Siegal, T; Neuwelt, EA; Pe‘er, J | Ophthalmology                                      | 2002 | 140 | 7.78          |
| Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina | Tamura, H; Miyamoto, K; Kiryu, J; Miyahara, S; Katsuta, H; Hirose, F; Musashi, K; Yoshimura, N | Investigative Ophthalmology & Visual Science        | 2005 | 138 | 9.2           |
| CNTF promotes survival of retinal ganglion cells after induction of ocular hypertension in rats: the possible involvement of STAT3 pathway | Ji, JZ; Eljaman, W; Yip, HK; Lee, VWH; Yick, LW; Hugon, J; So, KF      | European Journal of Neuroscience                     | 2004 | 136 | 8.5           |
| Outcome of intravitreal triamcinolone in uveitis                           | Kok, H; Lau, C; Maycock, N; McCluskey, P; Lightman, S | Ophthalmology                                      | 2005 | 136 | 9.07          |

(Continued)
| Title                                                                 | Authors                        | Source Title                      | Publication Year | Total Citations | Average per Year |
|---------------------------------------------------------------------|--------------------------------|-----------------------------------|------------------|-----------------|-----------------|
| Intravitreous anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy | Simo, R; Hernandez, C        | Diabetologia                      | 2008             | 135             | 11.25           |
| Incidence of endophthalmitis related to intravitreal injection of bevacizumab and ranibizumab | Fintak, DR; Shah, GK; Blinder, KJ; Regillo, CD; Pollack, J; Heier, JS; Hollands, H; Sharma, S | Retina-the Journal of Retinal and Vitreous Diseases | 2008             | 134             | 11.17           |
| Diabetes-enhanced tumor necrosis factor-alpha production promotes apoptosis and the loss of retinal microvascular cells in type 1 and type 2 models of diabetic retinopathy | Chin, HS; Park, TS; Moon, YS; Oh, JH | Retina – The Journal of Retinal and Vitreous Diseases | 2005             | 133             | 8.87            |
| Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy | Oshima, Y; Sakaguchi, H; Gomi, F; Tano, Y | American Journal of Ophthalmology | 2006             | 133             | 9.5             |
| Complications of intravitreal injections                             | Sampat, KM; Garg, SJ          | Current Opinion in Ophthalmology | 2010             | 133             | 13.3            |
| Biodegradable microspheres for vitreoretinal drug delivery           | Herrero-Vanrell, R; Refojo, MF| Advanced Drug Delivery Reviews    | 2001             | 132             | 6.95            |
| Triple therapy for choroidal neovascularization due to age related macular degeneration – Verteporfin PDT, bevacizumab, and dexamethasone | Augustin, Aj; PulS, S; Offermann, I | Retina -the Journal of Retinal and Vitreous Diseases | 2007             | 132             | 10.15           |
| Electrophysiologic findings after intravitreal bevacizumab (Avastin) treatment | Maturi, RK; Bleau, LA; Wilson, DL | Retina – The Journal of Retinal and Vitreous Diseases | 2006             | 131             | 9.36            |
| Rapid improvement of rubeosis iridis from a single bevacizumab (avastin) injection | Davidorf, FH; Mouser, J; Derick, RJ | Retina – The Journal of Retinal and Vitreous Diseases | 2006             | 129             | 9.21            |
| Posterior vitreous detachment induced by microplasmin               | Gandorfer, A; Rohleder, M; Sethi, C; Eckle, D; Welge-Hussen, U; Kampik, A; Lutbert, P; Charteris, D | Investigative Ophthalmology & Visual Science | 2004             | 128             | 8               |
The top 100 manuscripts originated from 16 different countries, with about half of them (52 manuscripts) originating from the US. Other countries of origin included Germany (n=15), Japan (n=6), Australia (n=6), the UK (n=4), Canada (n=3), France (n=2), China (n=2), Spain (n=2), Venezuela (n=2), and Belgium, Brazil, Israel, Lebanon, the Netherlands, and South Korea (n=1 each).

The mean number of authors was 6.1±3.4, with a median of 5 and a range of 1–21. Only one manuscript was published by a single author. There were 16 authors who had more than one first or last authorship on a paper in the top 100 list. These authors are listed in Table 2.

The top 100 manuscripts on intravitreal injections were published between 1974 to 2014. When further divided by decades, there were only two manuscripts published before 1990, 14 manuscripts were published between 1990–1999, 74 manuscripts were published between 2000–2009, and 10 were in 2010 or later. There was no correlation between year of publication and the total number of citations, but a significant correlation was found between later year of publication and a higher mean number of citations per year (P=0.0004).

Almost half (49) of the top 100 manuscripts on intravitreal injections were clinical studies which were conducted on human patients. Of these, 32 (65%) were prospective studies, 14 (29%) were retrospective studies, and three (6%) were observational studies. The number of eyes/patients analyzed in these clinical studies varied between 1–26,905, with a median of 26. Nine (18%) of the studies included 100 or more eyes/patients, while eight (16%) included fewer than 10 eyes/patients. Another 38 manuscripts were basic science papers, conducted on animal eyes or tissues under laboratory settings. The remaining 13 manuscripts included seven reviews, two meta-analyses, and four case reports.

The top 100 manuscripts on intravitreal injections covered a wide variety of topics. Most (60) of the manuscripts were focused on retinal diseases, including diabetic retinopathy (DR) and DME (n=23), neovascular AMD (n=20), RVOs (n=5), retinal ischemia and retinopathy of prematurity (ROP) (n=5), vitreomacular traction (VMT) and macular hole (MH) (n=2), proliferative vitreoretinopathy (PVR) (n=2), polypoidal choroidal vasculopathy (PCV) (n=1), retinitis pigmentosa (RP) (n=1), and lymphoma (n=1). There were also four manuscripts on uveitis and three manuscripts on glaucoma. Nine manuscripts were focused on complications of intravitreal injections, such as intraocular pressure elevation and endophthalmitis. The remaining 24 manuscripts focused on topics other than the injections themselves or specific clinical conditions, such as pharmacology and pharmacokinetic studies on intravitreally injected drugs (n=9), research on the effect of pathways and cytokines other than anti-VEGF and steroids.

### Table 2: Authors Who Had More Than One First or Last Authorship on a Paper in the Top 100 List

| Author Name | Number of First/Last Authorships |
|-------------|---------------------------------|
| Jonas, JB   | 8                               |
| Degenring, RF | 4                              |
| Spaide, RF  | 4                               |
| Billson, FA | 3                               |
| Gillies, MC | 3                               |
| Puliafito, CA | 3                             |
| Rosenfeld, PJ | 3                            |
| Tano, Y     | 3                               |
| Aiello, LP  | 2                               |
| Arevalo, JF | 2                               |
| LaVail, MM  | 2                               |
| Lightman, S | 2                               |
| Maranan, L  | 2                               |
| Panda-Jonas, S | 2                        |
| Schaermeyer, U | 2                        |
| Scott, IU   | 2                               |

### Table 3: The Topics of the Top 100 Most-Cited Manuscripts on Intravitreal Injections Included in This Study, in Descending Order of Frequency

| Topic                                      | Number of Papers |
|--------------------------------------------|------------------|
| Diabetic Retinopathy                      | 23               |
| Age Related Macular Degeneration           | 20               |
| Complications of Intravitreal Injections   | 9                |
| Pharmacokinetic Studies                   | 9                |
| Cytokines and pathways (not anti-VEGF/steroids) | 8           |
| Retinal Vascular Occlusion                | 5                |
| Retinal Ischemia and Retinopathy of Prematurity | 5            |
| Prematurity                                | 5                |
| Uveitis                                    | 4                |
| Glaucma                                    | 3                |
| Drug Mechanism of Action                   | 3                |
| Vitreomacular Traction                     | 2                |
| Proliferative Vitreoretinopathy            | 2                |
| Drug Delivery Techniques                   | 2                |
| Gene Therapy                               | 2                |
| Polypoidal Choroidal Vasculopathy          | 1                |
| Retinitis Pigmentosa                       | 1                |
| Lymphoma                                   | 1                |
(n=8), mechanisms of action of intravitreally injected drugs (n=3), novel drug delivery techniques (n=2), and gene therapy (n=2). These topics are presented in Table 3.

The agents studied in the top 100 manuscripts on intravitreal injections were numerous, but the majority of the manuscripts (75 of them) included anti-VEGF agents (pegaptanib, bevacizumab, ranibizumab, or aflibercept; n=38) or steroids (dexamethasone, triamcinolone, or fluocinolone; n=37). The most common anti-VEGF agent was bevacizumab (n=27; 71%), and the most common steroid was triamcinolone acetonide (n=29, 78%). The remaining 25 manuscripts included other intravitreally injected agents, such as ciliary neurotrophic factor (n=6), ocirplasmin (n=2), methotrexate (n=1), and other factors and antibodies that are not in clinical use.

Discussion

Over the past 15 years, intravitreal injections have become a mainstay in the practice of ophthalmology in general, and especially in the treatment of retinal diseases. Their excellent safety and efficacy profiles proved them to be superior to previous treatments, and they have very rapidly gained popularity and became the most commonly performed procedure in ophthalmology. This is the first bibliographic study focused on intravitreal injections, although it should be noted similar works have been done on macular imaging by optical coherence tomography (OCT) and pars plana vitrectomy. However, in contrast to these two key techniques that have also revolutionized the practice of ophthalmology, the evolution and acceptance of intravitreal injections has been much more rapid.

All manuscripts in the top 100 list were in English, and most of them were published in leading Q1 journals in Ophthalmology (n=67), with the most common country of origin being the USA (n=52). These findings are comparable with previous bibliographic works in ophthalmology.

This is not surprising, as the leading journals are based in the USA and published in English, and their manuscripts are likely to be more cited.

The majority of the top 100 manuscripts on intravitreal injections were published in the decade between 2000–2009 (n=74), with relatively few published prior to 1999 (n=16) or after 2010 (n=10). The first explanation for this finding is that the 2000–2009 decade was the time in which the pivotal studies that established the clinical efficacy of intravitreal injections of anti-VEGF agents (as well as steroids) were published. The works that introduced agents such as bevacizumab, ranibizumab, and triamcinolone acetonide as therapeutic modalities for numerous retinal conditions became landmark papers, with a high rate of citation. This is also reflected in the fact that most of the top 100 manuscripts included these drugs (n=75). A second explanation for this finding is related to the timing of publication. Relatively few studies published before 1999 have focused on these issues, and most of the works from that time that made it into the top 100 list are laboratory experiments, animal studies or small series, that have laid the base for the larger clinical trials of the 2000–2009 decade. Additionally, it is possible that older papers that are expected to have more citations, may have been undercited as they became common knowledge, forgotten, or refuted. In our study, there was no correlation between year of publication and total number of citations, indicating that older papers were not necessarily quoted more frequently than newer ones. Studies published after 2010 require a very high rate of citations per year in order to be included in the top 100 list, as is reflected by the significant correlation between the year of publication and mean number of citations per year (P<0.001). This is compatible with the fact that to achieve a high number of citations comparable to older publications, newer publications have to be cited more often each year since their publication, a phenomenon that was also reported in previous works.

Most of the top 100 manuscripts were focused on retinal diseases (n=60), the most common being AMD, DR, and DME. Also, half of them were clinical studies including human patients. These findings are not surprising, and intravitreal injections are primarily used for the treatment of these common retinal diseases, and have had a huge clinical impact for countless patients with numerous conditions. On the other hand, it is important to note that a significant portion of the top 100 manuscripts is focused on other diseases, novel drug delivery techniques, gene therapy, as well as new therapeutic agents administered by this route, indicating that intravitreal injections are not only integral to the current practice of ophthalmology, but also to ongoing research and development, and will likely continue to be an essential part of ophthalmology in the future.

There are several limitations to this study. We acknowledge that using different databases and search-engines, with different limitations and search definitions, would have resulted in a different list of 100 most cited
manuscripts. Our search methodology included all publication types, as citation rates apply to both original research articles as well as reviews, meta-analyses, and other publication types. We also note that the number of citations is not an objective measure of a paper’s quality, accuracy, or validity, but rather of its influence and acceptance in the field. This concept also has its limitations, as newer papers take time to accumulate a high citation rate, and older papers may become less cited with time as they become common knowledge or irrelevant. Therefore, we emphasize that this is our list of the 100 most cited papers on intravitreal injections, and not necessarily the best 100 papers. Another limitation is that self-citation was not excluded, as it would have been very complicated to determine this separately for each author in the 100 most cited papers. This is not a significant limitation, as self-citation has been reported to have a low influence on the total citation rate.

This bibliographic analysis depicts the rapid evolution of intravitreal injections and their effect on ophthalmology, as they transformed from a relatively rare procedure to the most common therapeutic modality in ophthalmology, matching the introduction and rapid prevalence of anti-VEGF agents administered by this route. The list includes many landmark papers and papers by leaders in the field, that have together driven the development of this technique that has truly revolutionized the practice of ophthalmology.

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