New developments in the treatment of corneal ectatic disorders

Addendum

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Developing a new treatment modality takes approximately 17 years from bench to bedside.[1] During this period, many experiments will fail, only a few will be successful, and about half of the successful products will eventually find their way into clinical practice.[1] The unmet need of keratoconus (KC) patients allowed for faster corneal collagen cross-linking (CXL) adoption within six years of the proof-of-concept and its first clinical application.[2,3] However, there was still much to learn and challenges to overcome along the way. Corneal CXL has evolved into a booming scientific field with many different research groups and as many perspectives, and a variety in success of implementing innovative ideas into clinical practice. The work presented in this thesis occupies a small niche in this academic field and focuses on:

- Improving existing protocols, increasing CXL safety and decreasing patients' burden (**Chapters 2, 3, and 4**). **Chapter 2** endorses the excellent success rate of current Riboflavin (RF) and ultra-violet A (UVA) CXL, found in our clinical study to be approximately 90%. For this 90% of patients, we suggest increasing safety in **Chapter 3,** as we show it is safer to reduce RF impregnation time. **Chapter 4** introduces a proof-of-concept for a novel treatment protocol that potentially reduces patients' burden.
- Developing a new CXL treatment modality to overcome the limitations of current options (**Chapters 5, 6, and 7**). Despite the great success rate, **Chapter 2** shows that 10% of patients exhibit a progression of KC despite CXL treatment. It is this 10% that warrants further investigation towards alternative treatment modalities. **Chapter 5** shows the stiffening capabilities of the alternative CXL method WST11 and near-infrared (NIR) CXL. **Chapter 6** demonstrates its long-term capabilities, and **Chapter 7** its resistance to enzymatic digestion.

In 2020, the Dutch National Institute for Public Health and Environment ('RIVM') predicted healthcare expenditures would increase by 2.8% annually until at least 2060.[4] About one-third of this increase can be attributed to population ageing. The other two-thirds are due to increasing healthcare accessibility, better and more frequent diagnosis, and new treatment options. As this growth in healthcare expenditures is not sustainable, political and societal solutions are sought. This prediction levies a responsibility on the medical and scientific communities to increase awareness of costs and pay more attention to cost-effectiveness. Riboflavin/UVA CXL is cost-effective, with rising effect rates as long-term results on CXL become available.[5,6] Godefrooij *et al.* calculated personnel costs account for 88.1% of the total costs.[7] Thus, reducing treatment time would directly minimize treatment costs. **Chapter 3** shows treatment time can be safely

reduced by 20 minutes, resulting in an approximately 15% reduction in treatment costs in a Dutch tertiary setting.[7] In **Chapter 5**, we show in an animal model that WST11/NIR CXL may further decrease treatment time to 1 minute only. Reducing treatment time also allows to treat more patients. Especially within the developing world, where KC prevalence is high while access to healthcare is scarce, this could result in a greater number of patients receiving adequate treatment. Furthermore, although RF costs only account for 3.4% of the total treatment costs, competing CXL modalities may also reduce material costs through free market forces.

Riboflavin/UVA CXL has been shown to effectively arrest KC progression, as illustrated by the significant reduction in corneal transplantations for KC since its introduction into clinical practice.[8] Where in 2003, RF/UVA CXL was first applied for KC, it has expanded over the years to photoactivated chromophore for infectious keratitis CXL (PACK-CXL), scleral CXL for myopia control, and other indications as discussed in **Chapter 8**. In traditional corneal CXL, WST11/NIR CXL may offer a solution to a select number of KC patients unfit for or unresponsive (i.e., 9.3% of patients, following **Chapter 2**) to RF/UVA CXL. However, current research heads towards individualized and targeted CXL, which aims to maximize treatment effect in the most affected regions of the cornea. Due to its favorable safety profile as compared to RF/UVA CXL, WST11/NIR CXL is more suited for such targeted approaches. Similarly, the safety profile of WST11/NIR may prove beneficial for emerging research areas such as PACK-CXL and scleral CXL for myopia. Two fellow PhD-researcher in our group, Judith Veugen and Demi Vogels, continue to research WST11/NIR CXL on these respective topics.

Patients may directly benefit from the protocol adaptations for RF/UVA CXL suggested in **Chapter 3**. **Chapters 5, 6, and 7** contribute to the general understanding of CXL and have broadened the scope by adding WST11 and NIR to the crosslinking armamentarium. While RF/UVA CXL was rapidly incorporated in KC management due to the absence of alternative treatment options, novel CXL modalities will have to meet the outcome of RF/UVA CXL. **Chapters 5, 6, and 7** are a scientific contribution to the rapidly evolving field of CXL, with **Chapters 5, and 6** showing practical advantages of WST11/NIR over current RF/UVA CXL protocols, and **Chapter 7** providing a direct comparison between RF/UVA and WST11/NIR CXL, with similar outcomes. Next, randomized controlled trials will have to show whether clinical outcomes of WST11/NIR CXL can equal or exceed that of RF/UVA CXL.

REFERENCES

1. Kirchner Jo Ann E, Smith Jeffrey L, Powell Byron J, Waltz Thomas J, Proctor Enola K. Getting a clinical innovation into practice: An introduction to implementation strategies. *Psychiatry Res*. 2020;283(June 2019):112467. https://doi.org/10.1016/j.psychres.2019.06.042
2. Spörl Eberhard, Huhle Michael, Kasper Michael, Seiler Theo. Erhöhung der festigkeit der hornhaut durch vernetzung. *Ophthalmologe*. 1997;94(12):902-906. http://www.ncbi.nlm.nih.gov/pubmed/9487761
3. Wollensak Gregor, Spoerl Eberhard, Seiler Theo. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135(5):620-627. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=36457967
4. Vonk RAA, Hilderink HBM, Plasmans MHD, Kommer GJ, Polder JJ. Toekomstverkenning zorguitgaven 2015-2060 : Kwantitatief vooronderzoek in opdracht van de Wetenschappelijke Raad voor het Regeringsbeleid (WRR). Deel 1: toekomstprojecties. *Heal care Expend foresight 2015-2060 Quant Prelim study Req Sci Counc Gov Policy (WRR) Part 1 Futur Proj*. Published online 2020. https://rivm.openrepository.com/bitstream/10029/623734/1/2020-0059.pdf%0Ahttp://hdl.handle.net/10029/623734
5. Godefrooij Daniel A, Mangen Marie Josee J, Chan Elsie, et al. Cost-Effectiveness Analysis of Corneal Collagen Crosslinking for Progressive Keratoconus. *Ophthalmology*. 2017;124(10):1485-1495. http://www.elsevier.com/locate/ophtha
6. Salmon HA, Chalk D, Stein K, Frost NA. Cost effectiveness of collagen crosslinking for progressive keratoconus in the UK NHS. *Eye*. 2015;29(11):1504-1511. http://dx.doi.org/10.1038/eye.2015.151
7. Godefrooij Daniel A, Van Geuns Pepijn, De Wit G Ardine, Wisse Robert PL. What are the costs of corneal cross-linking for the treatment of progressive keratoconus? *J Refract Surg*. 2016;32(5):355. http://www.ncbi.nlm.nih.gov/pubmed/27163622
8. Godefrooij Daniel A, Gans Renze, Imhof Saskia M, Wisse Robert PL. Nationwide reduction in the number of corneal transplantations for keratoconus following the implementation of cross-linking. *Acta Ophthalmol*. 2016;94(7):675-678. http://www.ncbi.nlm.nih.gov/pubmed/27213687