The approval of ranibizumab (Novartis Pharma AG) marked a significant change in treatment outcomes for exudative age-related macular degeneration (AMD), and established a new standard of care for the treatment of this disabling disease. Although monthly injections of ranibizumab resulted in the highest efficacy, concerns were raised regarding potential ocular and systemic safety risks, and feasibility and costs. Alternative regimens attempting to achieve similar efficacy with fewer injections of ranibizumab have been explored. In the PIER and EXCITE studies mean best-corrected visual acuity (BCVA) improved after three initial monthly injections; however, this declined during the subsequent fixed-quarterly injection phase. Trials investigating pro re nata (PRN) regimens also showed loss of mean BCVA from the peak value reached after the monthly initiation phase. The rationale of the PRN regimen was to individualize the antiangiogenic treatment in exudative AMD after observing in the failed EXCITE and PIER Trials that up to 40% of patients had a favorable outcome with a relative low number of injections. Therefore it was thought that the PRN regimen could identify the good responders from the poor responders, in order to avoid overtreatment. The PrONTO study suggested that this approach could be useful. However, these results could not be replicated at a larger scale in the SUSTAIN Trial. The CATT Study revisited the PRN regimen, although it also failed at 2 years as curves of mean BCVA started revealing from month 9. At 24 months, the mean BCVA of patients treated with PRN ranibizumab was of +6.7 ETDRS letters, versus +8.8 ETDRS letters in patients treated with monthly ranibizumab, representing a relative improvement of 28%.

In addition, in the PRN regimens despite the monthly follow-up the recurrences may be very aggressive, without being able to anticipate them properly, and secondly, as the SUSTAIN Study demonstrated, recovery of VA after the injection is usually lower than the amount loss in the recurrence, and the longer the time between the relapse and the previous injection the less recovery. Furthermore, the good compliance of the monthly follow-up, mandatory on the PRN regimens appears to be unlikely to occur in daily practice outside the strict protocols of the Trials.

Since there is no ideal individualized treatment one has to chose between 2 positions: a) protect and do not overtreat the good responders, with the risk of undertreating the poor responders (reactive regimens), or b) to protect the non responders with the risk of overtreating the good responders (proactive regimens). Between the 2 options, the amount of risk of total vision loss is by far much larger in the first one.

The clue of the higher efficacy of the proactive treatments may rely in the fact of treating ahead of the disease activity, avoiding recurrences, and not running after them with reactive regimens trying to solve their consequences. The treat and extend regimens may provide enough proactive treatment avoiding the limitations of the reactive regimens such as the PRN but avoiding the burden and overtreatment that may occur with the fixed monthly regimen.