Stopping Clinical Trials in Inflammatory Bowel Disease During the COVID-19 Pandemic Is Not a Responsible Act

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Abstract

The intense competition for resources to combat COVID-19 has greatly reduced access to health care for patients with other diseases. After the disastrous overrun of hospitals through COVID-19 patients in some jurisdictions, availability of resources for ‘elective’ medical procedures, including care for the chronically ill, has been greatly reduced in many places as a pre-emptive measure before or during the blooming of infection clusters. Pharmaceutical companies have either stopped recruitment or even cancelled ongoing clinical trials in chronic diseases. Pre-emptive triage and its impact on medical ethics is discussed in the framework of care for inflammatory bowel disease.

Key Words: Crohn disease; ulcerative colitis; drug development; registration trial; ethics; regulatory trials.

1. COVID-19 and IBD

The COVID-19 pandemic puts enormous pressure on health care, especially when the illness comes to those individuals already suffering from chronic diseases. Whereas it appears that COVID-19 related morbidity and mortality are mainly affecting older adults with pre-existing cardiovascular, metabolic, or respiratory comorbidities, it is apparent that the paediatric, adolescent, and adult populations are at risk too, although with lower incidence rates. Little is known about the role of chronic inflammatory diseases, including inflammatory bowel disease [IBD], as a comorbid risk factor for COVID-19. In the general population, IBD affects children, adults, and the elderly with two typical age peaks of onset, in early adulthood and around 50 to 60 years of age. At the current time, there are only anecdotal reports of COVID-19 in patients with pre-existing IBD. International registries are now collecting cases in which COVID-19 has developed in the setting of IBD. IBD represents an entity with a large unmet need for more effective therapies. An estimated 2 000 000 individuals in Europe and 3 500 000 people in North America suffer from the two main entities, Crohn’s disease and ulcerative colitis. Even the most effective medical interventions deliver much less than 30% efficacy in terms of induction and maintenance of symptomatic and endoscopic remission. When it comes to more stringent endpoints, including control of inflammation markers and histological healing treatment, efficacy rates are even less. Modern therapeutic options for IBD have been developed at considerable costs for research and development, costs which have been passed on to consumers and payers as among the most expensive therapies available for chronic diseases. The high costs are justified by the large impact of IBD on quality of life and social functions. Affecting more than 10 million people worldwide, the overall value of this therapeutic indication totals to more than EUR 30 billion [USD 32.4 billion] in 2019.
2. IBD, a Battleground for Therapeutic Drug Development

The combination of unmet needs and opportunity for profit has resulted in IBD becoming a competitive battleground for scores of new pharmaceutical developments competing for a potential step innovation in efficacy. Because of this competition, it has become extraordinarily difficult to recruit sufficient numbers of patients into clinical development programmes, with recruitment rates as low as 0.1 patient/site/month. The other major challenge for recruitment into IBD clinical trials has been ongoing use of placebo arms, such that patients refuse participation in the trial for fear of being randomised to placebo, which they perceive as inferior or even harmful. To address these challenges, clinical trials have been offering open-label extensions and rescue arms for individuals who complete a sufficiently long exposure in the controlled observation period. These open-label extensions have become a lifeline for many of the complicated patients who have exhausted all approved therapeutic options and who have responded to a new therapy in its pre-regulatory approval stage.

3. The Challenge for Pharmaceutical Companies

Pharmaceutical manufacturers face interesting challenges during the COVID-19 pandemic, which on the one hand threaten integrity of the observed data for therapy responses and side effects, and on the other hand may result in new side effects resulting from the interaction between COVID-19 and investigational medicinal products [IMP]. The reactions of pharmaceutical companies to this situation are widely disparate. Some companies support the continuation of recruitment and treatment with their IMP [and even relax the rules of therapy continuation or access to open-label drug despite missed endpoint assessments like endoscopies], and other manufacturers have decided to either halt recruitment or even discontinue ongoing therapies with experimental drugs. We have seen trials in early phases that were abandoned, recruitment that was temporarily stopped, and discontinuation of ongoing therapies including the open-label phase of long-term extension cohorts. This is unfortunately in line with major institutions shedding regular care for the chronically ill and the elderly by concentrating the resources for the care of incoming COVID19 patients which are expected in high numbers. At many medical centres, the clinical trial staff even have been instructed to work from home or take paid leave until the pandemic passes.

4. The Death Toll and Triage

The shutdown of elective care by health care providers adds an important second aspect, in which the discontinuation of ‘elective’ medical care by health care providers and the denial of clinical trial support by sponsors amplify the effects of one another. However, it is difficult to quantify the actual collateral damage that may have been caused by reduction of non-COVID-19-related healthcare services. Using other chronic diseases as an indicator [eg, chronic heart, vascular, and metabolic diseases], it may be suspected that reduction of elective procedures and access problems to non-COVID related health care services may result in a disproportional death rate. However, the result of the epidemiological perspective is inconclusive and highly dependent on regional jurisdictions. Whereas overall excess mortality rates in Lombardy/Italy [in comparison with expected deaths inferred from the previous years] between March 20 and April 20 were highly increased, with a significant proportion of excess death rates being caused by non COVID-19 indications, in Germany no clear signal of an excess mortality has been seen in the demographic statistics. [Figure 1A]. This is in significant contrast to an excess death rate largely caused by COVID-19 in England and Wales. [Figure 1B]. Across selected European nations, the excess death rate was estimated at 149 447 from Week 10, and as of Week 18, by the EUROMOMO statistical collaboration. Therefore, significant heterogeneity caused by differences in healthcare systems and environmental conditions will impact on any conclusions about the needs for shutdown measures and their resultant effect on health care.

Pre-emptive triage has been discussed at length during times of war, as an effort to free up beds well ahead of time before large battles are expected to produce scores of wounded soldiers. The danger of applying this concept in health care and to clinical trials is not only the potential harm to the individual seeking care under such circumstances, but also that such triage may negatively influence our daily standards of medicine. The shift from patient-centred practice to patient care guided by public health considerations creates great tension. Such prioritisation in anticipation of urgency but without the actual firm knowledge of an inevitable and inescapable situation is dangerous. It bypasses considerations of the individual in need in favour of the perceived coming needs of the population as a whole. These efforts are reminiscent of considerations about worthiness of individual life under the pressure of scarcity of resources, strategies that had terrible impact on societies in the years before and during the Second World War on both sides of the Atlantic. As a consequence of these behaviours, subsequent clinical medical ethics doctrine developed protection of the chronically ill, the weak, and the elderly, and treatment of each individual as an ‘end-in-himself’ or ‘end-in-herself’. The subsequent clinical medical ethics and research ethics principles became the centrepiece for delivery of care and performance of human subject research. During times of war and, we suggest, during this pandemic, we are in danger of violating these principles and harming the individual patients while succumbing to sweeping and unchecked changes in clinical trial design and continuity.

5. Need for a Critical Assessment

Whereas we share the notion of desperation and organisational turmoil, we have great concern about the decision of members of the pharmaceutical community to walk away from active clinical trials unless there is a defined scientific reason [eg, an interaction term between SARS-CoV-2 infection and a certain mode of action of an IMP]. In the ethical assessments of trial protocols, risks, benefits, and unmet needs are carefully weighed before a clinical trial is approved. Although individual benefit cannot be promised to the participants of clinical studies, clinical equipoise demands that any arm of a late-stage IMP trial must be sufficiently likely to provide benefit. It therefore follows that withdrawal of such trials and extension arms without direct and clear reason to do so is exposing patients to avoidable harm.

The regulatory bodies in both Europe and the USA have addressed the challenges to clinical trials during the COVID-19 pandemic, and offer a variety of solutions for investigators. The European Medicines Agency [EMA] has acknowledged this as follows. Extraordinary measures may need to be implemented and trials adjusted due to e.g. trial participants being in self-isolation/quarantine, limited access to public places [including hospitals] due to the risk of spreading infections, and health care professionals being committed to critical tasks. Therefore, EMA, EC and HMA strongly support the efforts of the Good Clinical Practice [GCP] Inspectors’ Working Group for developing a harmonized EU/EEA-level guidance.
to mitigate the negative effects of the COVID-19 pandemic on the conduct of clinical trials.\textsuperscript{13}

With the release of a specific Guidance on the Management of Clinical Trials During the COVID-19 [Coronavirus] Pandemic\textsuperscript{13} the EMA has acknowledged that the rules of GCP may need to see some relaxation to take incompleteness of observations and documentations into consideration which are unavoidable under the restrictions imposed on health care for the patients suffering from diseases other than COVID-19. The U.S. Food and Drug Administration [FDA] has issued similar general considerations, noting that it is to ‘assist sponsors in assuring the safety of trial participants, maintaining compliance with GCP, and minimizing risks to trial integrity during the COVID-19 pandemic’.\textsuperscript{14} In its guidance, the FDA acknowledges the need to re-evaluate clinical trial participation on a case-by-case and patient-by-patient basis, and encourages consideration of alternative means for monitoring and communication which reduce the need for travel to medical centres or to undergo additional testing. However, recommendations remain vague and case-by-case decisions are postponed into the future without pre-specifying any criteria; thus many sponsors feel the need for more clarifications. It would be a timely undertaking for the stakeholders to use the experiences gathered in this pandemic in order to prepare and to agree to harmonised, detailed guidance regarding how to conduct trials during national or international catastrophes. More precise and clear statements of what is and is not allowed, with the primary goal of providing maximum care to patients, would ease the positions of sponsors for making far-reaching decisions of protocol modifications.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Weekly death rates in Germany versus England and Wales from 2017 to 2020. Data were calculated from daily death rates published by the German statistical office\textsuperscript{8} and the UK Statistics authority. The graph shows death rates for each calendar week starting at calendar Week 2 for 2017–2020. \textbf{[A]} Whereas there is no excess death visible in Germany for 2020 during the COVID-19 pandemic, one can see excess death during calendar Weeks 8–14 in 2018. This time frame coincides with an influenza wave that hit central Europe. \textbf{[B]} In contrast to Germany, the impact of COVID-19 in England and Wales in 2020 is clearly visible between calendar Weeks 14 and 20. The lower two lines [green and violet] show the death by COVID-19 and the excess death by non COVID-19 causes that add up to the general excess in mortality.}
\end{figure}
6. Access to Health Care

Adapting the narrow rules in which clinical trials are conducted to the actual capabilities of health care [eg, access to endoscopies] and infrastructures [eg, availability of courier shipments to central laboratories] during the pandemic has represented in many instances an unavoidable necessity to modify protocol-defined procedures. Such modifications may impact on patients’ safety [eg, by using video consultations instead of physical visits with laboratory controls] and, especially in phase III clinical trials, may compromise the power to detect pre-specified endpoints [eg, missing endoscopies or histologies]. An interesting solution may be the development of framework rules for the implementation of unblinded disease and safety monitoring committees that could provide guidance to sponsors and regulators about how to conclude important programmes after the pandemic ends. This will allow for correction of ambiguities caused by temporary protocol modifications and incomplete treatment observations.

The reduced or limited availability of trial-specific health care resources also prompts an important discussion about feasibility of endpoint assessments. This discussion has to be led on both the level of the trial conduct [where endoscopy may be difficult to schedule during the pandemic] and the level of practical interventions and testing [where the translation of trial procedures to health care may be difficult due to long-term restrictions for access to certain procedures]. We need to discuss whether treatment endpoints like mucosal healing, which require endoscopy and biopsies, can still be used to examine patients in an environment stressed by chronic COVID-19. Therefore, the experiences during the present COVID-19 pandemic should result in accelerated development of validated biomarkers to replace some or all of the morphological assessments used for treatment guidance by investigators and regulatory bodies.

We work with the patients suffering from IBD and will continue to work with them—neither can their disease walk away nor shall we. Patients depend on new and unlicensed substances as an important resource for their therapy, and we consider it unethical to discontinue their clinical trial treatments at this difficult time as a first option. We can and should factor in the uncertainty of an interaction between a new therapy and SARS-CoV-2, but to avoid the issue entirely by withdrawing the patient from trials or discontinuing the trials is premature.

7. Tasks for the Future

Without a doubt, it is time to develop a responsible and unified position to the continuation of clinical trials in chronic IBD during the COVID-19 pandemic. We urge pharmaceutical companies, health care providers, and regulators not to abandon our chronically ill patients or clinical investigators during these challenging times. Instead, we believe that during these current and unprecedented challenges, appropriate resources should be focused on the development of novel and ethical solutions to clinical trial monitoring and endpoints.

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Conflict of Interest

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Author Contributions

SS wrote the first draft. All other authors added to the text and made substantial contributions to the writing and the reference list. There RE no data that had to be generated or processed for this article and no patients were involved.

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