Patient expectations in the clinical investigation of the first use of cortisone in rheumatoid arthritis: historical vignette

The development of a new treatment modality necessarily means first in human use and brings with it the responsibility to both protect the patient and provide knowledge or benefit that is generalizable to others. Although their motivations and backgrounds vary, researchers and patients both share the excitement of discovery and the consequences of study participation. We report the first use of cortisone in rheumatoid arthritis in 1948, which created great hope when it was developed and applied. The tensions of the study environment created by patient and investigator expectations as well as the effect of the drug led to a complex dynamic, which provided useful lessons for all involved and still affects clinical investigation today.

KEYWORDS: clinical trial ■ cortisone ■ history ■ rheumatoid arthritis

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Into the 1940s, clinical therapeutic trials were carried out informally. A detailed study protocol was not written. The trials were empiric; the mechanisms of action of the drugs being tested were seldom understood. The concept of informed consent by patients entering trials was poorly developed. Agreement to participation in an experimental trial was verbal and rarely documented in detail in the patient's record. Discussions regarding trials with patients were often, although not always, superficial. Patients were not expected to understand the details of the study. Furthermore, the risks and hazards related to the testing were unknown. It could be anticipated that misunderstandings would occur under these circumstances. Although reports of side effects of the drugs investigated were recounted in the literature, few instances of patient reactions to favorable or adverse responses have appeared. We describe an early patient whose reaction to unexpected adverse effects of the drug under study was marked and sustained. The lessons from this early experience are guideposts for understanding the concepts of patient education and informed consent for today.

Case report

The first patient to receive cortisone treatment for rheumatoid arthritis was a 28-year-old woman who was seen initially at the Mayo Clinic (MN, USA) on February 15, 1948 for an outpatient consultation [1]. The patient complained of swelling in multiple joints of 3.5 years duration. Previously, the patient had been treated with prostigmin, penicillin and streptomycin, all with transient benefit, but with continued joint swelling, stiffness and functional limitation. The patient had been placed on intravenous gold therapy and had received a total of approximately 2.5 g, given intravenously 50 mg weekly by the time of visit. The family history was unremarkable. The patient was married and had a young child.

Examination revealed active synovitis in multiple joints and moderate changes of rheumatoid arthritis on radiographs of the hand joints. Recommendations for further treatment included salicylates and a regimen of "diet and physical therapy." Apparently, an approach to treatment of rheumatoid arthritis based upon Dr Philip Hench's observation that the symptoms of arthritis were ameliorated in patients who developed jaundice was discussed with the patient [2]. After returning home, the patient wrote to Dr Charles Slocumb, a Mayo Clinic staff physician: "I want to thank you, Dr Slocumb and all those on S-10 who were so nice to me. … Dr Slocumb gave me a great deal of encouragement and hope. Even though the jaundice may not help, I feel I can still obtain relief, if I need it. Please let me know when you can use me for a "guinea pig," otherwise, this letter needs no answer, since you are both very busy. Sincerely yours..." Shortly another letter was received which contained the following: "Dear Sirs, two months of the specified time have now elapsed and I am still quite anxious to become a research patient for the jaundice treatment … I can be there in short notice; however, I wonder if you now know approximately when you can use me … I will be most happy to cooperate in any way and certainly do appreciate the opportunity. My only wish is the sooner, the better. Sincerely yours…"

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In May, 1948 the patient returned for 2 weeks of outpatient physical therapy. In another letter dated July 9, 1948 the patient wrote: "Dear Sirs, at the risk of repeating myself for the umpteenth time, I repeat: My arthritis is much the same and I am still just as anxious to try the jaundice." The patient sent another similar letter on July 20, 1948, reiterating the desire to come to Mayo Clinic for the treatment.

The patient returned to Rochester, MN, USA, and was admitted to Saint Marys Hospital on July 26, 1948. On examination, the patient appeared mildly depressed and "moves slowly and stiffly." There was marked swelling in multiple joints of the hands, elbows, shoulders, knees and feet. The (Westergren) erythrocyte sedimentation rate was 75 mm/h, the serum protein was 8.97 gm/dl and albumin 4.35 gm/dl. Because of a moderately elevated alkaline phosphatase and bromsulphalein grade 2 retention, concern was raised regarding hepatitis; a liver biopsy was performed and was essentially normal.

A trial of lactoferrin to induce jaundice was initiated on August 6, 1948 [3]. There was no treatment response and by September 20, 1948, the joints were "worse than they have been," according to physician notes. The patient was anxious to try another therapy. A small amount of 'compound E' or cortisone had just become available for a trial and Dr Philip Hench made a decision for the patient to be the first to receive the drug [1]. A dose of 100 mg/day by intramuscular injection was initiated on September 21, 1948. Physician notes that day remarked that the patient "…can hardly get out of bed, walked only once."

On September 23, 1948, the record indicates that the patient "feels much less muscle soreness this AM and feels stronger, appetite good this AM." The patient stated, "Breakfast almost a pleasure." The note continues: "Rolled over and turned off radio with ease for first time in weeks – no more trembling of knees when moving. … Most improvement subjective and in muscles. Joints only slightly better." By September 24, 1948, joints were "50% plus better." Appetite was "very good." On September 24, 1948, Dr Hench noted, "If … progress continues, would maintain … on present high dose to obtain full effect, if the medicine holds out. Then, sometime soon, reduce dose to maintenance dose, to find level of effective potency." Subsequently joint counts were obtained two- to three-times per week.

To evaluate the anticipated systemic effects of compound E, serial 24-h ketosteroid measurements were obtained in urine at baseline and fell dramatically after September 21, 1948, consistent with the effect of administration of exogenous steroids.

By September 29, 1948, the dose of compound E was reduced to 50 mg/day and then to 25 mg/day. By October 7, 1948, the patient complained of increased musculoskeletal discomfort and was not sleeping as well. By October 8, 1948, for the first time, a note appeared in the medical record that "patient discouraged." The dose was increased to 50 mg/day on October 13, 1948 and then 2 days later to 50 mg twice daily with improvement. At that point, facial puffiness was becoming very apparent. By November 19, 1948, the patient had developed facial hirsutism and acne. Later, the dose of compound E was adjusted, to 50 or 100 mg/day, depending on symptoms.

Through Christmas and New Year 1948/1949, the attending physicians reported that the patient "Retained 75–80% improvement, with injections changed to three times per day." Side effects worsened and in January, 1949 the patient began complaining of visual blurring, ear ringing and jitteriness. These side-effect symptoms abated over approximately 1 week with dose reduction. However, with worsening arthritic symptoms, by the first week of February, the compound E dose was increased to 300 mg/day to duplicate the response to this dose seen in two other patients who had subsequently been started on the drug.

By this point, the patient's depression, which had been present at baseline and especially marked in the morning, began to worsen noticeably. The patient also complained of discomfort in the hips, which waxed and waned, and burning sensations in the joints, which extended "to the fingertips" and "into fingernails." On March 4, 1949, the patient is recorded as saying: "Never had rheumatoid like this before." The patient became edematous without evidence of renal failure. By March 11, 1949, the patient felt that, although the arthritis was approximately "50%" improved compared with prior to starting compound E, there was generalized aching in "regions other than joints – bone and muscles in contrast to joints. … This is something different." Physician notes include comments such as: "Disability is now different." Patient states: "Shape of face is different, have more fuzz." The physician notes record that her "Complexion is darker, pouchy and upper lip and nose fuller, acne worse, weakness, amenorrhea, osteoporosis also prominent factors." Patient "…prefers arthritis to what I have now, but I hope to get things straightened out. … I am not myself now – cry, nervous,

can't concentrate, etc." The patient commented that "in AM, feels more depressed, … have silly obsessions." A consulting endocrinologist noted that the patient demonstrated marked evidence of adrenal cortical hyperfunction.

On March 22, 1949, a psychiatric consultation was obtained. Phenobarbital was started to reduce the patient's anxiety and depression. The patient was "worried about everything" and not wanting to talk to anyone and having "frantic feelings inside." By March 29, 1949, the patient commented, "My fear complex changed to a hate complex," and was "depressed and crying, discouraged about looks and fear of crippling." The patient reported poor sleep and symptoms appeared to worsen over the subsequent month. The patient became more withdrawn and stated, "I lost my mooring and am quite reaching now to get my anchoring." The preexisting anemia worsened and the erythrocyte sedimentation rates were again elevated. Blood transfusions were administered and gold therapy was reinitiated by the end of April 1949.

The relationship between the patient and the medical staff deteriorated. Dr Slocumb noted on May 10, 1949, that the patient's mother, who had become very critical of the treating physicians, "… is again very antagonistic in attitude, but says nothing to us." He continues, "The patient's spouse called and expressed … understanding of family situation and thanked us for the work done and wants … [the patient] to remain under our care." Dr Hench noted on that day, "This is a tragic situation – the conversion of a fine, intelligent, grateful, affirmative, super cooperative patient into a doubting, antagonistic … [person] who wishes to warn people "not to use E until they learn how to use it properly, all because of … [the patient's] almost insufferable animosity to all that we have done and try to do! The only redeeming feature is that the [spouse] apparently appreciates all we have done." He continues that the "Patient's mother was quite uncivil when we tried to say goodbye – ignoring us coldly and purposefully." This was the final note from this prolonged hospitalization.

Following hospitalization, Dr Slocumb noted in the record, "Until toward the end of … [her] hospitalization, … [the patient] was an ideal patient and then certain influences, chiefly from the maternal side, changed the picture, to our great regret. We have no doubt that matters will clarify themselves. We are particularly anxious to hear regarding … [the patient's] progress…" A subsequent note from Dr Slocumb to the family physician indicated that the Mayo Clinic physicians were "very concerned about the patient's reaction to the hospitalization. We are very sorry that the family feels as they do toward us and have been respectful of their feelings since last spring. We want to be of any help to you and to … [the patient] at any time we can and shall continue our interest in … [the patient's] progress." Dr Slocumb noted that other early cortisone patients had written to the patient as well, without response and "all concerned have wondered whether … [the patient] ever got the notes and have suspected that the notes were intercepted by the mother and answered by her … I wish, indeed, we could make direct contact with … [the patient], but in view of the unfortunate episode, it would seem better for … [the patient] to either write to us first or at least let us know directly that … [the patient] would be glad to hear from us."

The patient wrote to Sister Pantaleon, head nurse on the Rheumatology Service, on January 17, 1950, thanking her for "…your precious time you gave to me. I often tell my mother you kept me alive. I am still ill just now. I am regaining a little strength and am a little less sore. I have such kind doctors, whom have tried so hard to help me and to undo all of the cruel things (underlined in the card) that were done to me." The thank you card is signed and, in parentheses, the statement, "written for … [patient's name] by … [patient's] mother" is added. A second card from January 17, 1950, was written to another early cortisone patient hospitalized during this same time period and given to the physicians at Mayo Clinic. It states, "My Dear, … [patient's name], I was so glad to get your card and note. I can never express in words what your friendship and kindness meant to me when I was so sick, so discouraged and had my trust so betrayed by the Judas at Mayo." The letter goes on to state, "I am learning again to walk by the aid of a walker that my doctors advised. I still have a very long, hard climb to recovery. My doctors tell me I have very little, if any, of my old trouble… and my illness is caused by the reaction of having E forced on me (signed, …[patient's name], written by … [patient's name] mother for [patient's name])." A letter sent by the patient to another early cortisone patient at Mayo Clinic, [patient's name] in December of 1952 noted that the patient was now divorced and remarried. The patient had seen a physician at home who diagnosed lupus erythematosus. The letter stated that, "At the Mayo Clinic, they not only treated … [the patient] wrong but didn't even make the right diagnosis". Dr Hench noted that the mother now had "more ammunition with which to vilify those of us here".

A letter from the patient's home physician to Dr Howard Polley in May 1955 indicated that he first saw the patient on March 3, 1951. "There was some flushing over the malar areas. It was at that time, we found … [the patient] had clear evidence of disseminated lupus erythematosus. There were numerous lupus erythematosus cells demonstrated. The patient refused any cortisone therapy but reluctantly accepted some treatment with adrenocorticotropic hormone, which we continued all the time." The home physician reported that in November 1954, the patient was hospitalized with severe joint pain and pelvic pain and severe headaches. The possibility of subarachnoid or septic hemorrhage or septic meningitis was considered. Large doses of narcotics were required to control the pain. Intravenous penicillin and adrenocorticotropic hormone were given. On the afternoon of December 22, 1954, "…[the patient] became suddenly nauseated, began coughing up frothy-tinged sputum. The lungs were filled with coarse rhonchi. There was no question but that the patient was in acute pulmonary edema." The patient died at 11:55 p.m. on December 22, 1954. "Just what the terminal event was a little difficult to say. [The patient] had pulmonary edema and there is also a serious question whether … [the patient] did not have massive gastric hemorrhage from a probable ulcer." An autopsy was not obtained. Attempts to review the home hospital and physician's records were unsuccessful because they had been misplaced or lost.

Commentary

The decision to give this first patient compound E was certainly in part driven by the patient's persistence and insistence on receiving a new and more effective therapy for rheumatoid arthritis. After an initial visit at Mayo Clinic and later, the patient wrote letters expressing this desire. The medical staff considered the patient to be a good candidate to be the first to be given cortisone. The patient appeared cooperative and to understand the nature of an experimental trial. The patient may have appeared overly anxious to be a "guinea pig", but had an active progressive incurable disease. The diagnosis was well-documented. Patient relations with the medical staff had been excellent. A history of depression was noted on admission, but it was not considered severe. Dr Hench and the other rheumatology staff felt that compound E had a definite possibility of a favorable effect and indeed the response to treatment after the initial doses of cortisone were administered was dramatic and cause for great optimism that this drug could bring the disease under control. The risk of an immediate severe toxic reaction was low [3]. However, the long-term toxicities at the doses given were not known.

The complete explanation of the marked deterioration in patient–physician relations and development of hostility by the patient and the patient's mother may not be completely answerable. The degree of suppression of the arthritis by cortisone was unexpected and could have led to unwarranted expectations. After experiencing the first few days it would have been easy to conclude that an effective cure of the arthritis was a real possibility. These expectations were destroyed when symptoms returned on lower doses and adverse effects started to appear. The severity of the side effects was also unexpected and the patient was unprepared for them. The medical staff were also unprepared. Before giving cortisone, the length of time to develop side effects and their severity with the doses prescribed was completely uncertain. At that time, very little was known about the effects of exogenous cortisone in humans [4]. The history of depression was not recognized as a potential risk factor for psychological side effects.

Cortisone likely influenced the patient's emotional status and added to the patient's worsening depression, both magnifying the reaction to the side effects and diminishing the patient's ability to cope with them. The patient's mother compounded the effect by repeatedly critically expressing her concern regarding the side effects and the treatment. The hostility was not simply a transient manifestation while on higher doses of cortisone because it continued in correspondence years later. The patient's anger against the Mayo Clinic was not global, as the patient extended warm feelings to the hospital nursing staff after dismissal from the hospital. It appears possible that the unexpected occurrence and severity of the adverse effects, including the emotional reaction and the mother's reinforcement, is at least a partial explanation. Throughout the treatment period and later the physicians caring for the patient were obviously very concerned regarding the patient's welfare.

Could this unfortunate outcome have been avoided? This initial single-patient trial was carried out by the best intentions and standards of the 1940s. A detailed plan or treatment protocol was not written out. The concept of informed consent by patients entering trials was poorly developed at that time and there was no notation in the record of a discussion with the patient and relatives on the possible favorable effects or

the potential risks associated with the drug. The treatment was open-ended rather than for a defined period of time, after which an analysis of results could be carried out to help modify a possible future study. Only a small amount of drug had become available and the first trial was expected to be short term because of drug supply. Dr Hench hoped it would be enough to determine whether it caused a favorable effect on the arthritis, writing "…the use of these hormones should be considered an investigative procedure, not a treatment…" [5]. When the marked reduction in symptoms was observed and more cortisone was supplied, this resulted in relief of joint pains but also increased side effects. Subsequent to the patient's treatment, a more formal double-blind study was carried out, but this first patient to receive cortisone was not part of that study [6,7].

More modern practices not available at the time of formulating a detailed protocol with specific goals and durations of treatment may have prepared the investigators with a plan to deal with the unexpected severe adverse effects when they arose. A signed consent may have helped as an educational tool. The investigators cannot be criticized on these grounds, as these practices had not been developed at that time. Indeed, the concept of 'informed consent' was only introduced in 1957 in the case of Salgo versus Leland Stanford University Trustees [8].

Even if an informed consent had been available, it is clear that the patient's desire to be in a clinical trial, desire for improvement and the trust put in the treating physicians most likely would have led the patient to participate in the study. It is unclear from the clinical documents contained in the medical record how thoroughly the patient was informed of or understood these risks, nor even whether the treating physicians anticipated their full magnitude.

The tension between the trial goals and patient-care goals created a rift that was irreparable and which the Mayo Clinic physicians greatly regretted. How much the patient actually understood or felt regarding this tension between the goal of producing generalized knowledge for the advancement of medicine and the goal of the clinical care of the patient, which was to produce improvement in individualized care, is not certain. The early sense of help and trust that was also the basis for the enthusiastic participation of the patient in the clinical study turned to disappointment and rejection.

A thorough discussion with the patient and perhaps other interested persons regarding possible expected and unexpected outcomes and risks that the patient must be willing to accept as part of the participation in a research investigation may have helped the patient and the mother become partners in the trial and deal more evenly with the outcomes experienced while on cortisone.

Conclusion

The lessons learned from this initial use of corticosteroids in a patient with rheumatoid arthritis and certainly the experiences of other clinical investigators of the 1940s and later continue to be powerful instruction in doctor–patient relationships in practice and in clinical research. These experiences have in a positive way influenced the development of approaches and tools to address patient and investigator concerns and foster human subjects protection in the conduct of clinical trials.

Future perspective

The importance of human subjects protection in clinical research is today universally recognized and codified in documents such as the Helsinki Declaration. The improvement of processes for assuring subject rights and understanding and improvements in the design and conduct of clinical research are perennial responsibilities of the clinical research community. The subject–investigator relationship,

Executive summary

- Clinical trial development and conduct have evolved to include formal processes and expectations for study design, investigator responsibilities and human subjects protection.
- The first patient to receive cortisone treatment for rheumatoid arthritis was in 1948. The patient experienced considerable initial relief of symptoms, then relapse and with continued treatment, marked drug-related side effects. These side effects were frustrating and damaging to the patient–physician–investigator relationship.
- Modern practices, which were not available at the time, of formulating a detailed protocol with specific goals and durations of treatment as well as a signed informed consent, might have helped prepare the patient and investigators to deal with the adverse effects. The concept of informed consent was introduced in 1957.
- The lessons learned from this experience and other early clinical trials have led to better understanding of patient expectations and in a positive way helped to develop tools to address patient and investigator concerns, as well as foster patient and investigator protection in the conduct of clinical trials.

which often grows out of the patient–physican relationship, will always be an important component of this dynamic.

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▪ **Thoughtful, detailed treatment of the evolution of human subjects protection in the context of clinical studies.**