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ETHICS (CR MACKENZIE AND I DE MELO-MARTÍN, SECTION EDITORS)

The ethical challenges in rheumatology

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Abstract Ethical dilemmas arise with regularity, indeed daily, in the practice of rheumatology. As such, the practitioner must have the sensitivity and capacity to recognize them, reflect on their implications, and formulate responses directed at their mitigation. This article presents relevant ethical considerations (old and new) arising in the contemporary practice of rheumatology. A number of considerations stand out for their relevance to the rheumatic diseases. Conspicuous among these are the high costs associated with modern antirheumatic therapy, the complex relationship between physicians and the pharmaceutical industry, as well as challenges to the provision of care to patients suffering from complex chronic diseases. In this regard, patient autonomy is discussed, as is the need to insure for the provision of the time and resources for adequate patient education. The importance of such concerns goes beyond the patients' themselves extending to the future generation of physicians who we will educate.

Keywords Ethics · Rheumatology · Pharmacoeconomics · Autonomy · Pharmaceutical industry

Introduction

The rheumatic diseases are composed of a diverse assortment of challenging conditions, often of an inflammatory nature, treated with a complex array of therapies. In dealing with its attendant clinical responsibilities and research pursuits, ethical issues often arise in the field of rheumatology. Despite their frequency, ethical issues have not engendered much discussion in the rheumatic disease literature. A systematic review of this topic revealed a remarkably low rate (0.026 %) of published articles addressing the well-known bioethical model (autonomy, beneficence, nonmaleficence, or justice) [1]. MacKenzie et al. [2••] have recently rejuvenated this dialogue with an article on the perceived ethical issues among American rheumatologists. The study found that conflict of interest (overuse of infusion biologic therapy when self-administered medications are available), high cost of medications, the use of expensive radiographic imaging, and the practice of defensive medicine were the important themes identified in their survey. The arena of clinical research was felt especially fraught with ethical challenge (56 %), with lower rates reported in clinical practice (44 %), and in basic research (20 %). of defensive medicine were cited as the most common ethical issue in a practice setting [2••].

Within the various realms of practice, the rheumatologist may face ethical challenges in four areas; societal, face to face (with the patient), industry, and research. The goal of this article is to review emerging ethical challenges and discuss considerations for each.

Pharmacoecconomics

There is an array of biologic therapies in rheumatology with targeted mechanisms of action; however, rheumatologists face ethical challenges with regard to their use including access (through both government and insurance companies) and cost. In terms of actual costs, Bonafede et al. [3•] used US claim-based data to estimate the cost per treated patient for a variety of inflammatory conditions (rheumatoid arthritis, psoriasis, psoriatic arthritis, and/or ankylosing spondylitis) receiving a biologic response modifier, old and new (etanercept,

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abatacept, adalimumab, certolizumab, golimumab, infliximab, rituximab, or ustekinumab). Among the three anti-TNF agents (etanercept, adalimumab, and infliximab), the cost per treated patient across all four conditions combined in the first year after the index anti-TNF agent claim was $22,722 (US dollars) for etanercept, $23,170 for adalimumab, and $24,601 for infliximab. When etanercept was used as the comparator, the cost per treated patient for abatacept, certolizumab, golimumab, or rituximab ranged from 90 to 102 % relative to etanercept. The cost per treated patient was equivalent (100 %) for golimumab relative to etanercept in patients with psoriatic arthritis and 94 % for golimumab relative to etanercept in patients with ankylosing spondylitis. While we as rheumatologists understand how the different biologic therapies work and have evidence for their efficacy, there are times when the patient cannot access the medication, and this creates an ethical dilemma.

Further, such cost-effectiveness analysis is a valuable tool to use to decide if and when a treatment may be justified in our society. In a recent study by van der Velde et al. [4••], the group examined the cost-effectiveness of biologic therapies in different groups of patients with rheumatoid arthritis, using the willingness to pay threshold. This concept is understood as the maximum the decision-maker (the payer) is willing to pay for an extra unit of health effect [4••]. The values used were $50,000 per quality-adjusted life years (QALY) and $100,000 per QALY. In patients with no prior DMARD exposure, or who failed methotrexate monotherapy or sequential DMARD therapy, biologics were found not to be cost-effective at a willingness to pay threshold of $50,000 [4••]. In patients who failed methotrexate combination therapy or sequential administration of DMARDs, biologic therapy was found to be cost-effective in 14 of 35 comparisons (comparison to a DMARD sequence) at a higher willingness to pay threshold of $100,000/QALY [4••]. Thus, according to this methodology, it costs more to gain an additional health benefit from biologic sequence therapy. Thus, the investigators concluded that it was more cost-effective to treat patients first (early) with DMARDs and adding biologics later if a patient fails to respond [4••].

Consider the following case example:

A patient with end-stage renal disease from amyloidosis, due to ankylosing spondylitis, has been treated with a biologic by the rheumatologist; her renal function has stabilized and her back pain has remained about the same with the use of a biologic, which has been covered by her insurance company. After 6 months, her insurance company requires resapplication, and based on the marginal improvement of her Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, they reject the claim. You and her nephrologist (who is fully supportive of continued biologic therapy) write the insurance company in support of continued treatment; your other option is to apply through the Exceptional Access Program.

The ethical dilemma in this scenario surrounds the use of a costly medication for a secondary effect (improvement in her renal function). From the point of view of her ankylosing spondylitis, her back pain was only marginally improved. Should the rheumatologist continue to prescribe such a costly treatment for her condition?

Examined through the lens of medical ethics, this case challenges a central ethical paradigm, that is, justice. Justice, as a principle of medical ethics, addresses the notion of fair treatment, in this case whether the insurer's claim is a reasonable one [5]. In this case, as a rheumatologist, one must think of the costs of the care and critically review alternatives for this patient. Would it not be cost-effective to treat the patient with a biologic medication and keep her off dialysis? Or perhaps, as a less favorable (but much cheaper) alternative, prednisone could be used to control her inflammatory response; however, the side effects of long-term prednisone are numerous and detrimental. Another point to consider is how the government or insurance companies define medically necessary care or more specifically how they allow access to medications, such as biologics. Criteria have been established, the Exceptional Access Program (EAP) in Ontario is such an example, for the use of biologics which employ predetermined "response criteria" that allow for continued use of the biologic [6]. Yet, this is the best way to identify medical need for these medications, as criteria developed for populations may not fit well in a given patient. How are such dilemmas to be approached?

An approach to the resolution of this case is through advocacy, that is, support your patient. This may include writing a letter to the insurance company in support of your patient and explaining that the BASDAI is only one way for evaluating a response to therapy, citing how her laboratory indices (inflammatory markers, erythrocyte sedimentation rate, and C-reactive protein) had much improved. Another option would be to apply to the EAP program for the medication. A third, interim option would be a direct request for medication from the pharmaceutical company on compassionate release grounds.

Physician-pharmaceutical industry relations

Another important area of challenge for the rheumatologist, as with other disciplines, is relationships with industry. There is an ongoing critique in the literature [7, 8] about physicians' call of duty with respect to pharmaceutical relations. In the first review, Sah et al. [9••] describe the social psychology techniques used by the pharmaceutical industry to influence physicians' behavior and ultimately prescribing practices. The authors encourage physicians to remain at arms length with

pharmaceutical industry and call for further education to medical residents and physicians. In the study by MacKenzie et al. [2••], the most prevalent ethical issues arising in this domain were serving on the board of directors (76 %), participating in speakers bureaus (66 %), and consulting (61 %). Similarly, in unpublished work by McKeown et al. [10], the Canadian rheumatology population thought that serving on a company's board of directors was the common industry-related activity that posed an ethical challenge. Guidelines from governing bodies in the field are particularly useful, as they are continuously revised and updated accordingly [11, 12]. For example, the College of Physicians and Surgeons of Ontario has recently been working on new policy guidelines for physicians' interactions with the pharmaceutical industry and includes guidelines on industry gifts, continuing medical education, involvement in industry-sponsored research, and advisory boards.

Consider this scenario:

You have just started your rheumatology practice, and within the first 2 weeks of practice, your secretary states that a pharmaceutical representative would like to meet with you. You are in between patients and decide to think more about this after your clinic. As you are bringing in the next patient, you also overhear the pharmaceutical rep asking your secretary how she takes her coffee.

The ethical issue in the above case is the potential conflict of interest of the physician and his/her professional responsibilities with the industry representative. The industry representative has already asked the physicians' assistant to accept a small gift. The considerations are for the physician to critically review the potential relationship with the industry representative and what implications it has on his/her practice. It has been shown in the literature that accepting gifts from pharmaceutical representatives influences physician choice of which medication to use, even small gifts [7, 9••, 13]; indeed, acceptance of even small gifts influence physicians behavior in ways they themselves are unaware [13]. The pharmaceutical industry uses highly sophisticated techniques to influence physician behavior and do not necessarily have the best interests of the patients in mind. The physician needs to recognize the scope of the pharmaceutical industries' influence and understand why they might be inclined to accept a gift, even if a small one. Is this a sense of entitlement or is it a sign of career accomplishment or status? The physician needs to keep the fiduciary relationship between patient and physician in the forefront, guiding their decision-making and act in a way to maintain the trusting relationship with the patient. It has also been shown that the public, when surveyed, have mixed emotions regarding the acceptability of physicians accepting gifts from industry. When Canadian adults were asked this in a survey study, Holbrook et al. [14••] found that public opinion was evenly split from acceptable to unacceptable towards physicians accepting different gifts such as small gifts (e.g., pens or golf balls with advertising). Fifty-five percent (55 %) reported such behavior as acceptable with 44 % reporting it was not; similar responses were obtained when patients were asked about such practices as free dinners for doctors attending a talk given by a company employee (54 % acceptable/39 % unacceptable) or all expense-paid trips for the doctor to attend a medical conference (50 % acceptable/44 % unacceptable) [14••]. The negative impact of such behavior is that physician objectivity is compromised with patients, as upon learning of such practices, trust is lost [15]. With this, in mind, one of the potential solutions is to disclose to your patients what (gifts, samples, etc.) have been received. Yet, when rheumatologists were asked their opinion regarding such disclosure, only 51 % stated that they should divulge such activities. Further, even disclosure to your patients may not remove the bias that has already occurred. Therefore, physicians need to take a hard look at themselves and remember their moral obligation to the patient also understanding how they are role models to younger trainees. Thus, in this case, the physician has to consider his/her position critically, appreciating that the influence of even the smallest gifts may affect their judgment. Would he/she be able to defend their actions? Where does one cup of coffee lead to? While one can still meet with the pharmaceutical representative, the accepting of gifts is not acceptable.

Patient autonomy

A 57-year-old female has rheumatoid arthritis (RF and anti-CCP positive) with early erosions on her X-rays. Despite treatment with plaquenil followed by methotrexate and prednisone, she continues to suffer a great deal of pain. She is also depressed; her family physician believes she has overlapping fibromyalgia.

You follow her every 3 months for signs of clinical remission; however, on repeated visits, she continues to have at least two swollen joints and her laboratory indices show continued elevation of inflammatory markers; thus, in your judgment, she does not meet remission criteria. On triple therapy, yet shows signs of ongoing disease, you feel that moving to a biologic is indicated. However, she has hesitations, including the subcutaneous injections and worries about the treatment. In order to further explore her hesitations, you bring her back to clinic to discuss the issues. After repeated visits, she still does not want to pursue biologic therapy, even though you feel this would be the best treatment for her.

One of the fundamental principles illustrated in the above case is patient autonomy. This is understood as the right to self-government or self-determination or to take decisions regarding one's health into their own hands [5, 16•]. It allows patients' voice to be heard and them to be a partner in medical decisions, a model of health care that works within the biological, social, and psychological realms of the person. Each

person has different beliefs, values, and background experiences that influence their decisions when it comes to their health. As physicians, we need to accept this and work with patients to inform them about treatments, risks, and benefits. At times, the patient-physician relationship can become divergent as a patients' refusal of treatment may not be in line with what the physician feels is optimal therapy. The concept of patient autonomy has been expanded upon to include self decision-making based on the available resources, known as autonomous decision-making [17]. In an interesting paper by Townsend et al. [18], help-seeking behavior and the concept of autonomous decision-making was studied in a group of eight patients diagnosed with rheumatoid arthritis. The results show that patients normalized their symptoms, adapted to and contained their symptoms until they met with their general practitioner and eventually with a rheumatologist. The analysis also showed that due to lack of knowledge about rheumatoid arthritis and the need for timely treatment, autonomous decision-making was compromised [18]. Another participant felt under-equipped to make a fully informed choice about her treatment, illustrating a lack of consideration for the emotional needs of the patient and further need for support. Thus, steps need to be put in place (such as awareness, time and support during the medical encounter for education and self-management) for the patient to become an expert and a fully informed autonomous decision-maker. It is one ethical issue that the patient have autonomy in their medical decision; however, it is also another that the patient have the available resources to adequately attempt to make the decisions. Physicians also need to be supported in their role of appropriately addressing the patients' concerns and educating them about medications, side effects, support networks, and living with a chronic condition. In fact, time itself has been identified as an ethical issue; 22 % of Canadian rheumatologist felt that spending sufficient time with patients was an ethical issue [10]. The challenges of preserving autonomy in the setting of chronic disease are more fully discussed in the paper of MacKenzie and de Melo-Martin included in this series.

The rheumatologist may have different resources at their hands to help resolve this ethical issue. The physician can bring the patient back for repeat visits to further explore the concerns the patient has about the medication, or have a member of the allied health care team (advanced nurse practitioner) meet with the patient, or attend a support society education day (e.g., The Arthritis Society of Ontario). Importantly, the patients' autonomy has to be respected, even if that is refusal of the biologic therapy.

Conflict of interest

Lastly, a number of rheumatologists spend some of their time in research and a number of ethical issues are found within this realm of our field. When American rheumatologists were asked about ethical lapses (that is, failure to uphold an ethical standard that one reports to believe), more respondents said these occurred more often in clinical research as compared to clinical practice (28 versus 17 %). Sugarman et al. [19] provide a thorough review of ethical issues in clinical trials in rheumatology; he begins by addressing the concerns of enrolling patients (either treatment naïve patients or treated patients) into early phase clinical trials or prevention studies. He highlights the ethical considerations of testing novel therapies in early phase trials when standard or known treatments are available and perhaps deferred; for example, the inclusion criteria for enrolling in a particular study may deem that exposure to a standard DMARD therapy or intra-articular injections of corticosteroid must not have occurred in the last 6 weeks before starting the newer biologic therapy [19]. Thus, the physician may struggle with the treatment decisions for the patient; should he/she hold off therapy and hope the patient be enrolled in the clinical trial? Therapeutic equivalence trials are now conducted and are considered ethically acceptable to investigate a novel agent; the design involves starting the experimental therapy (in addition to baseline medications) in all patients, followed by a randomized "washout period" or continuation of the agents in responders and watching for a disease flare [19].

Consider the following example:

You are a clinician scientist and participating in an industry-sponsored research study evaluating a novel agent for rheumatoid arthritis. During your meeting with the company, the industry representatives begin to pressure you to agree to put a number of patients on their drug over the next X months. What are the ethical issues?

Firstly, this example illustrates a marketing technique used by the pharmaceutical industry to influence physicians and get physicians to commit to something. The example also illustrates the strong pressure exhibited by pharmaceutical industry which can influence the physician and negatively impact the process of informed consent. Drug companies may also approach a physician to enroll patients in post-marketing surveys or "seeding" studies; the latter is a study where patients may receive the medication free of charge on a short-term basis and clinicians may be reimbursed for enrolling them [19]. This creates a conflict of interest for the physician. Further, the information gained from this study may be questionable as the data is not always analyzed. Informed consent is a key ethical principle in research. In the above example, informed consent may be threatened as the physician may highlight the "novel therapeutic" agent, which is misleading to the patient.

Stating that a treatment is "therapeutic" is misleading when this is unknown at the beginning of a trial is discussed in the article by Sugarman et al. [19] and Romain [20] also discusses the vulnerability of patients with more severe disease, in that they may be more willing to participate in a research trial and sacrifice some aspects of their "personal care." He speaks of the concept of "therapeutic misconception", defined as the personal sacrifice patients may make by participating in research trials, without recognizing it either [20]. Clinicians must be mindful of the aspects of informed consent including explaining the potential risks and benefits to patients and allowing them opportunity to ask questions and clarification. Would the clinician in the above example pay close attention to these details if she/he was feeling external pressure from the drug company to enroll more patients? Informed consent is the key ethical protection given to potential participants in research studies, thus it must be adhered to with the upmost of integrity.

The above scenario illustrates the potential conflicts that can occur in clinical research, and the physician should recognize the potential for bias when enrolling patients into the trial. Thus, the physician should consider discontinuing interactions with this representative, hopefully without hindering the overall project or support for the project. The physician may consider discussing the situation with a data steering committee or a relevant institutional official.

Conclusion

The above cases illustrate some of the ethical challenges in rheumatology as a specialty and within medicine as a practice. Pharmacoeconomics is now a major concern in the field, and we have to be conscious of costs to society. Physicians are gatekeepers to medications, some more costly than others, and we have to think of the overall benefit to the person and society. Patient autonomy is complex in which adequate resources for both patients and physicians are needed to effectively support this basic tenet in medical ethics.

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Compliance with Ethics Guidelines

Conflict of Interest Emily J. Mckeown declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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