National Institute for Health and Clinical Excellence

Use of tumour necrosis factor alpha (TNF á) inhibitors (adalimumab, certolizumab pegol and infliximab [review]) and natalizumab for Crohn's disease

Royal College of Nursing

Introduction

With a membership of over 395,000 registered nurses, midwives, health visitors, nursing students, health care assistants and nurse cadets, the Royal College of Nursing (RCN) is the voice of nursing across the UK and the largest professional union of nursing staff in the world. The RCN promotes patient and nursing interests on a wide range of issues by working closely with Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations.

Response to consultation on Use of tumour necrosis factor alpha (TNF á) inhibitors (adalimumab, certolizumab pegol and infliximab [review]) and natalizumab for Crohn's disease

The Royal College of Nursing welcomes the opportunity to review this document.

What is the expected place of the technology in current practice?

The condition is treated according to site, activity and pattern following best practice and national /local guidelines. There is geographical variation and differences in practice depending on physician choice and available facilities. Infliximab and Humira are the only agents currently licensed for use in severe active crohn's disease but there are alternative agents available for use through clinical trials.

There are subgroups of patients with the condition who have a different prognosis from the typical patient; this includes those with previous malignancy, young children, patients with a history of TB and patients with previous sensitivity of Anti-TNF agents. Patients with fistulating disease may have an increased risk of intra abdominal or pelvic collections and sepsis. Therefore they have to be clear of infections prior to treatment being given because of the immunosuppressive properties of these drugs. All of these are at greater risk of potentially fatal complications following treatment. Patients at high risk of TB may require yearly chest x rays, whilst on treatment. We need to consider whether younger patients are at greater risk overall in terms of immunogenicity, developing other morbidity and mortality. The elderly are less likely to develop severe reactions and it may be less of a risk to treat this group of patients. Long term data is limited and delayed morbidity may well occur. The risk to the patient needs to be documented and serious consideration needs to be given to obtaining written consent from patients before treatment starts, in case of litigation.

Crohn's disease is not curable by surgery therefore patients my have disease recurrence which may require further surgical intervention. The consequences of further surgery can be extremely grave and carries the risk of short bowel syndrome. This would put patients at risk of requiring home parenteral nutrition, an intervention with co-morbidity from the presence of the line, and costs from frequent hospital admissions due to fluid balance problems and infections.

The treatment should be used in either secondary care or specialist infusion centres (or in primary care where emergency resuscitation facilities are available) so patients can be assessed and monitored by nurses who have knowledge of the side effects of the drug and access to facilities in case of emergencies.

Patients with fistulating disease without evidence of severe active disease may be denied funding as they do not meet current guidelines. This group of patients potentially miss out on life changing treatment and subsequently endure multiple examinations under anaesthetic with its associated complications.

However, infliximab is licensed for use in fistulising Crohn's disease and there is a substantial amount of evidence to support its efficacy for this complex disease group. Specialist advice must always be immediately available from those who are familiar with using the drug, in order to determine whether to continue with or stop the infusion should the patient start to develop acute or delayed side effects.

Occasionally specialist advice may be sought from other experts such as dermatologists when severe skin reactions i.e. urticaric vasculitis has developed. Often the IBD specialist nurse is asked to organise and 'watch over' the patient as well as being the point of contact for the patient and nursing staff administering the infusion.

Infliximab and Adalimumab are the only agents currently licensed. The general consensus with Infliximab is induction treatment at 0,2,6 weeks, although this may vary according to clinician choice, and may be given as episodic treatment in some centres. Adalimumab is licensed for treatment at 80mg at week 0 then 40mg EOW, although there is flexibility for dosing at 160mg week 0, 80mg week 2 and 40mg alternate weeks. This is dependant on the patients previous response to biologics and physician choice. Extra caution must be exercise if the higher dosing schedule is used due to the higher incidence if adverse reactions. Prophylactic corticosteroids are given in many centres prior to each infusion of Infliximab, although the type and frequency of this varies nationally. Adalimumab is licensed to be given with corticosteroids during the induction phase where there is no contraindication. Certolizumab and Natalizumab are still in clinical trial phase therefore experience is limited to those centres participating. The treatment does vary amongst clinicians, perhaps due to the availability of funding or resources. 'Maintenance treatment' in particular is limited in certain areas due to funding, despite the fact that without treatment, this group of patients would have limited medical options.

The decision to use the treatment may be made by one clinician or it may be made following a multidisciplinary team meeting.

The advantages and disadvantages of the technology

Infliximab is given intravenously. The speed of administration varies, and with some centres infusion takes place over as little as 30 minutes following 10 previous consecutive infusions without complication.

Infliximab may be the preferred drug of choice for those patients who are less likely to comply with treatment and need closer monitoring to assess their response to therapy.

Humira is given as a subcutaneous injection and has facilities in place via the manufacturers for the patient to self administer at home at the discretion of the treating physician.

Patients need to be carefully selected to ensure safe self administration of Humira and warned against overdosage when they are feeling unwell. Some patients report symptomatic relapse days before their next injection and may decide to inject prematurely.
The healthcare at home delivery service may be more convenient and cost effective for patients and the NHS, however, safeguards have to be in place to avoid accidental or intentional misuse of the drug or even sharing with other patients. Certolizumab Pegol is administered Subcutaneous but is still in clinical trial phase.

With regards to concomitant drug use whist taking Biological therapy, it is often recommended that patients take immunosupression (Azathioprine/methotrexate) concomitantly to prevent against antibody formation, where there is no contraindication or the patient has not been proven refractory.

Pre treatment rules state that patients must be free from infection as demonstrated by urinalysis, chest X-ray and routine blood tests. Female patients must also be on adequate contraception during treatment and for 6 months afterwards.

Best practice based guidelines would be helpful and enable pre-treatment counselling as well as allowing clinicians to use their clinical judgement according to emerging evidence based data. Protocols can be too prescriptive and become out of date quickly.

Response is assessed via clinical assessment and an improvement in the CDAI/Harvey Bradshaw. The drug would be discontinued if patients suffered an adverse reaction or no clinical response.
This emerging technology requires careful monitoring and a nationwide register needs to be devised (such as the TREAT registry in USA) of all those patients receiving anti Tnf agents would help to collate valuable data on each drug. This would help to inform all clinicians involved with treating inflammatory bowel disease patients receiving biological therapy.

Hepatosplenic T cell lymphoma is a rare but globally observed fatal complication which has been documented recently, yet did not become evident in clinical trials. Neurological disorders including demylinating syndrome have been reported, along with opportunistic infections and lupus.

Any additional sources of evidence

Somerville, M. Brooksby, A. Scott, G.I.
Rheumatology unit, Norfolk & Norwich University Hospital
Maximising the use of scarce resources: vial optimisation (2005)
Rheumatology, (2006) 45: 353 – 364

Observational data: See comments in next section

Implementation issues

All biological therapies are costly and units across the country are looking at ways of maximising the use of this treatment whilst ensuring that eligible patients are treated. Ways of reducing wastage of an expensive resource have been developed; such as sharing vials when preparing Infliximab infusions. By infusing several patients at the same time, we can reduce the number of vials used overall, instead of discarding the portion of the vial not required. The more patients infused at the same time, the greater the reduction in wastage. Safety measures have to be robust in order to prevent any errors or contamination and a sterile environment is ideal.

In order to minimise risk to patients the National Patient Safety Agency guidelines on injectable medicines recommends that Infliximab should be prepared in an aseptic environment. Whereas in practice it is usually prepared in a clinical ward environment by a registered nurse. Therefore a formal risk assessment needs to be made by each organisation which administers the drug, in order to identify measures to reduce the risk to patients.

NICE guidance would make the drug more easily available, particularly by getting funding agreement from primary care. Currently some hospitals have reported that funding is often refused for patients with Ulcerative colitis, despite it being a licensed indication, due to the fact that there are no NICE guidelines covering its use.

Guidance would provide patients with more treatment options other than surgery, which can be a traumatic, life changing event that could potentially be avoided or delayed by treatment with Infliximab.

Infliximab is an established treatment for Crohn's disease in secondary care; therefore no additional training/resources would be needed for its use in Colitis if it is given in the same clinical areas.

However, with respect to primary care, the appraisal should consider whether there are sufficiently skilled staff to administer and care for patients undergoing this treatment? If not, do we need to consider logistical issues such as training as well as raising awareness in primary care? As this is very much a secondary care based treatment patients have to rely on specialist staff for support and care. If this treatment becomes more common practice, then the wider health care community needs to be educated to deal with patient issues / side effects.